Nat. Volatiles & Essent. Oils, 2021; 8(5): 1344 - 1352

COVID-19 and Acute Kidney Injury: Fascinating Kidney Biopsy findings in a short Case Series

***Dr.Monali Rajendrakumar Sahu[1],*Dr. Sonali Dilip Wairagade[2],Dr. Shrikant V Mukewar[3], Ranjit S. Ambad[4] Dr. Nandkishor Bankar[5]**

[1]*Consultant Nephrology, Midas Multispecialty Hospital, Nagpur, Maharashtra*

[2]*Professor, Department of Kayachikitsa, DattaMegheAyurved Medical College Hospitaland Research*

[3]*Consultant Gastroenterology, Midas Multispeciality Hospital, Nagpur, Maharashtra*

4 Associate Professor Department of Biochemistry, Datta Meghe Medical College, Shalinitai Meghe Hospital &Research Centre Wanadongri, Hingana, Nagpur-441110, Maharashtra, India.

5 Associate Professor Dept. of Microbiology Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi (Meghe) Wardha

email id:sonaliwairagade@gmail.com

Abstract:

AKI has been observed as a common problem of coronavirus disease 2019 (COVID-19) on frequent occasions in patients with moderate to severe disease. These patients showed presence of proteinuria and microscopic hematuria. Outcomes of such patients are bad with higher mortality and many of those surviving have become dialysis dependent. Kidney biopsy features show variety of tubular and glomerular involvement with acute tubular injury being a common finding.

Methods: We evaluated clinical features of four patients at our institution who had COVID-19 and AKI, with proteinuria with or without hematuria and their kidney biopsy findings. We describe clinical presentation, histopathologic findings and further course of our patients.

Results: This study includes four patients with COVID 19 who had proteinuria and renalimpairment with two requiring dialysis. We performed kidney biopsy in all four patients. Allkidney biopsies showed acute tubular necrosis. Further, additional features were seen in 3patients including minimal change disease, pauci-immunecrescentic GN, and focal as well as Segmental glomerulosclerosis in each patient. In one patient electron microscopy was done to assess ultrastructural evidence of viral particles and it was negative.

Conclusions: Acute tubular necrosis was found in all our patients who suffered from COVID-19 with acute kidney injury. SARS-CoV-2 particles were not seen when one kidneybiopsy sample was subjected to electron microscopy.

Keywords: AKI (Acute Kidney Injury), COVID-19, Kidney Biopsy

Introduction:

Pandemic of severe acute respiratory syndrome coronavirus2(SARS-CoV-2) affected 114.6 million Worldwide causing more than 4 million deaths from the illness of coronavirus19 i.e. Covid-19. The disease predominantly affects lungs and respiratory airways and ifinvolves heart or kidneys simultaneously; it portends a further bad prognosis [1-3]. Individuals with diabetes, hypertension and pre-existing kidney disease are at risk of aggressive disease [4-7].Various mechanisms causing kidney injury have been postulated which include ischemia resulting from severe lung injury, cytokine storm due to increased levels in the circulation of pro inflammatory cytokines and bradykinin; and lastlySARS-CoV-2 affecting renal parenchyma directly.

Data of four patients is presented here; all four patients suffered from Covid-19 and had renal impairment, with proteinuria. Renal presentation was of acute kidney injury or acute kidney disease with dialysis requiring AKI in two patients. Kidney biopsy was done of all four patients at our centre. Clinical features, kidney biopsy findings and further course of all four patients were found to quite diverse as described below.

Case 1:

65 years old female was positive for Covid-19 PCR in January 2021, for which she was hospitalized and treated. Then in February last week she again developed shortness of breath, Her HRCTchest showed ground glass opacities with CT score of 22/25.She was hospitalized and was treated as covid pneumonia. Again March 3 rd week she had respiratory symptoms and she received treatment as percovid protocol. She developed bleeding per rectum, oliguria. And she had severe anemia and renal failure. She was started on haemodialysis and received two units blood transfusion. She came to us on 14 th May 2021. She had complaints of dyspoea on exertion, reduced urine output, vomiting, malena and bleeding per rectum since one week. There was no history of rash or hemoptysis. Physical examination revealed mild dehydration, tachypnoea and normal blood pressure of 120/80mmHg. She did not have peripheral edema and her systemic examination was unremarkable.

Investigations:

Haemogram showed value of haemoglobin to be 7.2 g/dL (11.5–13.5 g/dL), white cell count of 13000/ mm3 (4500–11000/mm3) and platelet count of 141 000/mm3 (150 000–450000/mm3). C reactive protein value was normal. Serum sodium was 128mmol/L (135–145mmol/L) and potassium was 2.0mmol/L (3.5–5.1 mmol/L). Kidney function test showed Blood urea of 116 mg/dL (<48 mg/dL) and serum creatinine was 4.1 mg/ dL (0.26–0.42 mg/dL) with estimated glomerular filtration rate (eGFR) of 11.15 ml/min/1.73 m^2. Serum uric acid level was 4.5 mg/dL (2.7-7.3 mg/dL), serum phosphorus level was2.1 mg/dL (2.8–4.5 mg/dL) and calcium was 8.2 mg/dL (8.6–10.3 mg/dL). Urinalysis showed proteinuria, microscopic hematuria and UPCR (g/gCr) was 2.62.Ultrasound abdomen showed bilateral lyechogenic kidneys with cortico medullary differentiation maintained. Her upper GI endoscopy, colonoscopy and capsule endoscopy showed no active bleeding, ulcer, abnormal vessel or obvious mass. Her antinuclear antibody (ANA) and double stranded DNA (DsDNA) were negative. Her ANCA results were obtained and she was found to be cANCA positive with negative pANCA. After stabilization her kidney biopsy was done. Kidney biopsy showed acute tubular necrosis of moderate grade with mild IFTA of 10%. In addition it showed pauci-immune crescentic glomerulomnephritis. 56% of glomeruli had cellular crescents in and44% of glomeruli had fibro cellular crescents. So, kidney biopsy features were consistent with cANCA positivity, and granulomatosis with polyangiitis (GPA). Her previous respiratory involvement was likely fleeting pulmonary infiltrates which was considered to be due toCovid-19 and so was treated with IV methyl prednisone, to which she had responded.

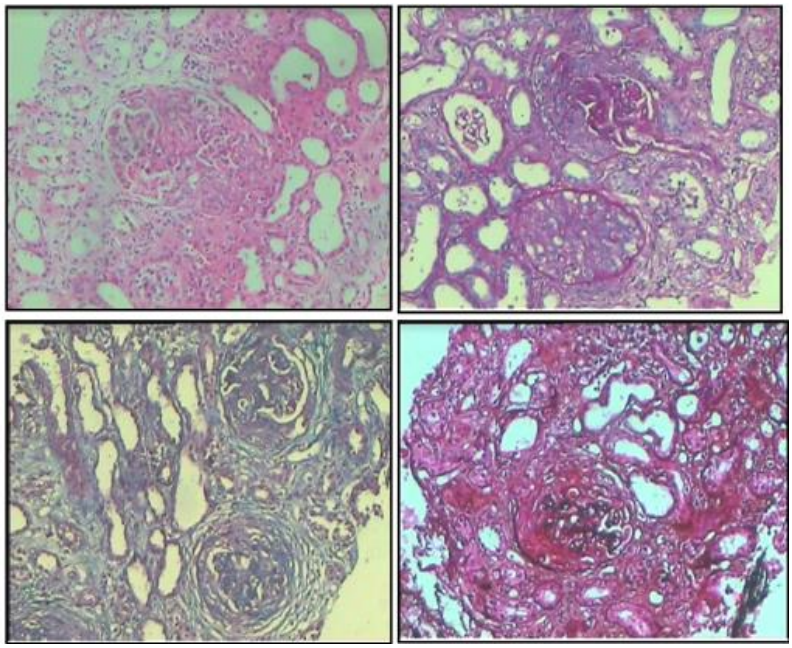

Figure1: Kidney biopsy showing pauci immune crescentic glomerulonephritis, findings consistent with cANCA positivity and acute tubular injury with mild IFTA - 10%.

Case 2:

32 year old male was known case of Coronary artery disease with LBBB in ECG and related hyperkinesias with reduced left ventricular ejection fraction. He presented with abdominal pain,

swelling all over body and reduced urine output. He had no history of fever. Physical examination revealed pallor, tachypnoea and blood pressure of 120/80mmHg. He had Peripheral edema and respiratory examination revealed bilateral basal rales and abdominal examination revealed tender hepatomegaly.

Investigations:

Biochemical examination on admission revealed haemoglobin of 10.6g/dL, white cell count of 7.3x10 ^{9} /land platelet count of 234 K/ul. KFT revealed blood urea 145mg/dl and serum creatinine of 8.7 mg/dl and GFR of 7.25ml/min/1.73m ^{2}. Sr. sodium was 128 mmol/Land Sr potassium was 5.2mmol/L, uric acid level 8.3mg/, serum phosphorus 5.1mg/dLand calcium was 8.9 mg/dL. Urinalysis showed proteinuria, microscopic hematuria and UPCR(g/gCr) was 1.67. Ultrasonography (US) demonstrated and bilaterally echogenic kidneys with cortico medullary differentiation maintained. His antinuclear antibody(ANA) and double stranded DNA (DsDNA), cANCA and pANCA were negative. After stabilization his kidney biopsy was done. Next day, he developed hypoxia so his RT-PCR was repeated and came to be positive. HRCT chest revealed bilateral ground glass opacities with CT score of 9/25. Creactive protein was 27 mg/L(0.3 to 10 mg/L), serum ferritin was 362ng/mL(0 to 250 ng/mL)and D dimer was 1967(< 0.50). He was treated for Covid-19 and haemodialysis continued. After 3 more sessions of dialysis on alternate days, his urine output gradually improved. His kidney biopsy showed 9 glomeruli, all normal by light microscopy and severe acute tubular injury (ATN) with cellular and necrotic debris in tubules. Interstitium was edematous with mononuclear cellin filtrate. His serum creatinine came down to1.2mg/dland was discharged. He is under follow up and 6 weeks post discharge his UPCR is 0.12 and serum creatinine is 0.8mg/dl.

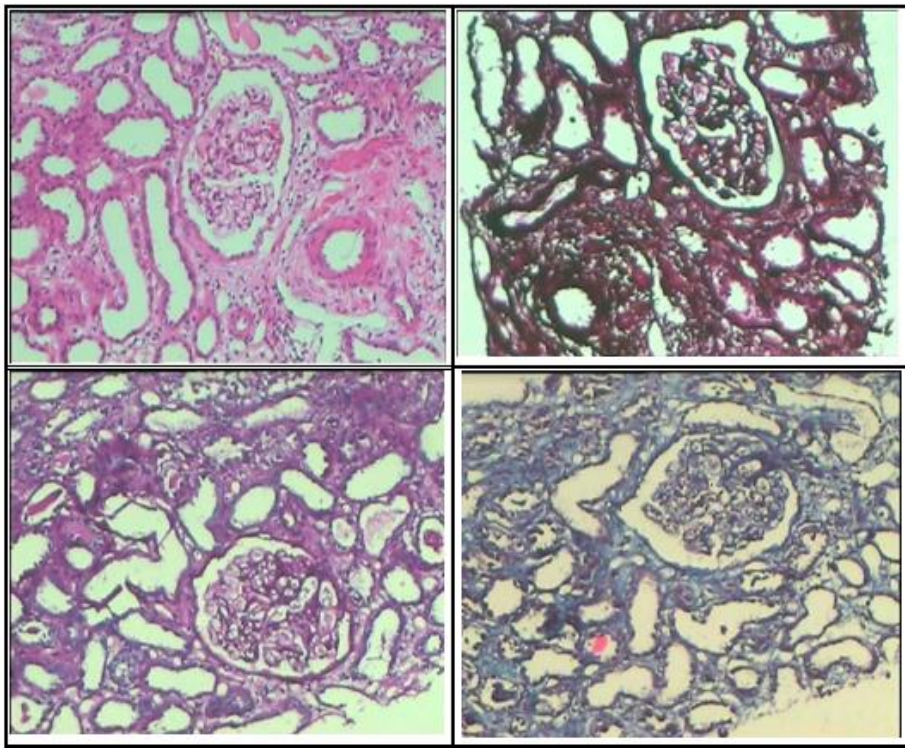

Figure 2: Kidney biopsy of case 2 showing severe acute tubular injury (ATN).

Case 3:

23 year old male was treated for Covid-19 in April 21, he was RT-PCR positive and had CT score of 7/25. He came to us after 5 weeks with complaints of swelling all over body and reduced urine output. Physical examination revealed normal blood pressure. He had puffiness of face and bilateral lower limb edema. Systemic examination was unremarkable.

Investigations:

Biochemical examination on admission revealed haemoglobin of 10.5g/dL, white cell count of 7.3×109/Land platelet count of 314K/uL. KFT was normal with blood urea of 37mg/dL, serum creatinine of 1.1mg/dLand, eGFR of 94.12mL/min/1.73m^2. Sr sodium was 128mmol/L and potassium was 4.8 mmol/L. Uric acid level was 6.1 mg/dL , phosphorus level was 3.7mg/dLand calcium was 9.2md/dL. Urinalysis showed presence on albumin ndipstick and UPCR of 2.96. Ultrasound abdomen showed bilaterally echogenic kidneys with corticomedullary differentiation well maintained. His kidney biopsy was done and itshowedfeatures of minimal change disease with mild mesangialhypercellular variant. Mild ATN was also seen. He is started on oral corticosteroids.

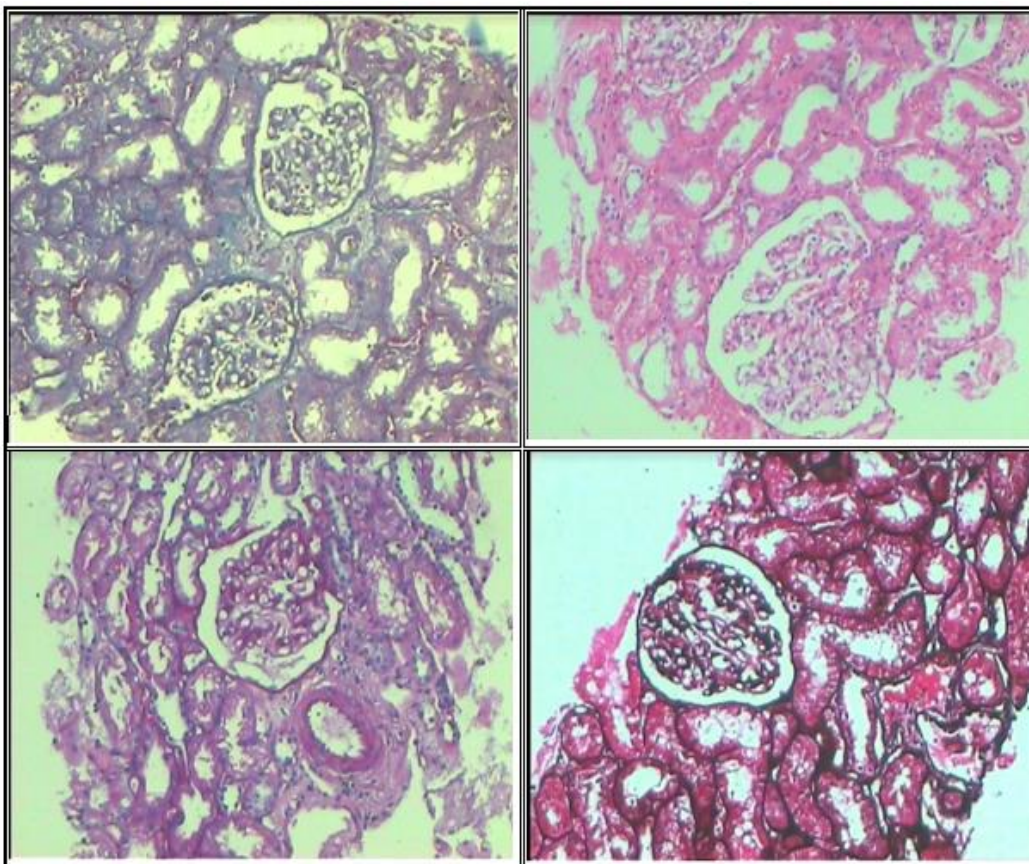

Figure 3: Kidney biopsy of case 3 showing features suggestive of minimal change disease with mild mesangialhypercellularity variant.

Case 4:

55 year old male, known case of hypertension was treated for Covid in February21,he was RT-PCR positive and had CT score of 10/25.

Investigations:

Biochemical examination on admission revealed haemoglobin of 11.4g/dL, white cell count of 9×10^{9}/L.1000/mm3 and platelet count of 21K/uL. He had renal impairment with blood

Urea and creatinine of 46mg/dL and 2.4mg/dL respectively and eGFRof29.27 mL/min/1.73m^{2}.Sr sodium was132mmol/Land potassium was 4.2mmol/L. His serum uric acid, phosphorus and calcium levels were within range and were 5.6mg/dL, 4.1mg/dLand9.3 mg/dL respectively. Urinalysis showed proteinuria, microscopic hematuria and UPCR(g/gCr) was 1.01. Ultrasonography (US) demonstrated and bilaterally echogenic kidneys with corticomedullary differentiation maintained. His antinuclear antibody(ANA) and double stranded DNA(DsDNA), cANCA and pANCA was negative. In the fifth week postcovid when serum creatinine was still 1.9 with eGFR 38.82mL/min/1.73m^{2} kidney biopsy was performed. Biopsy showed features suggestive of Focaland Segmental Glomerulpathy with global sclerosis in isolated glomeruli. In addition, features of focal acute tubular injury and benign hypertension were noted. He is under follow up and is treated as chronic kidney disease.

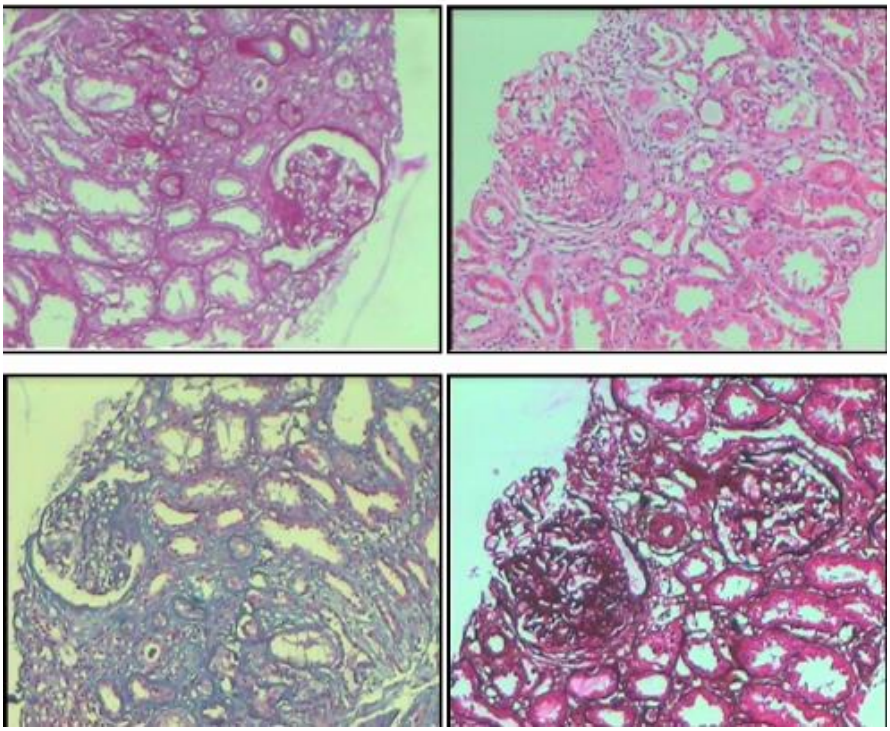

Figure 4: Kidney biopsy of case 4 showing Focal & Segmental Glomerulosclerosis - NOSType with Focal Acute Tubular Injury and changes of Benign Hypertension.

Table 1:

Data of four patients with COVID_19 and AKI, includes demographic details, relevant clinical information, further progress and kidney biopsy findings

Clinical Data	**Patient Number**			
	1	**2**	**3**	**4**
Age	65	32	23	55
Sex	Female	Male	Male	Male
DMII/HTN present	HTN	Nil	Nil	HTN
Admission Scr, mg/dl	4.1	8.7	1.1	2.4
Proteinuria, g/d	2.62	1.67	2.96	1.01
Hematuria	Present	Present	Absent	Present
Relevantserologies/laboratory values	cANCA positive	-	-	-
Vasopressor requirement	Nil	Nil	Nil	Nil
Highest Sr Creatinine(mg/dl)	12.4	8.7	1.3	2.4
Additional contributors of AKI (other than COVID-19)	No	ARBS	No	InjArachitol
Kidney size, cm, L,R	9.6,9.4	11.2, 10.9	11, 11.3	10.2, 10.5
Reason for kidney biopsy	HD requiring acute kidney	HD requiring AKI &	Nephrotic range proteinuria	Severe AKI & significant

	disease &proteinuria	proteinuria		proteinuria
Post Biopsy complications	Perinephric hematoma	Nil	Nil	Nil
Kidney biopsy diagnosis	PauciimmuneCrescentic Glomerulonephritis, ATN & mild IFTA 10%	Severe ATN	MCNS- Mild mesangialhypercellular variant& mild ATN	FSGS plus mild ATN
Renal consequence	Dialysis dependent	Dialysis required but complete renal recovery achieved	Improved with corticosteroids	Kidney function improved partially but CKD

Discussion:

Initial information of COVID-19 publicized a low incidence of acute kidney injury (0.5%–15%).Conversely as data about disease advanced it was comprehended that AKI occurrence was much higher. Hirsch etal. established the incidence of aki to be37% after reviewing health records of close to 5000 patients[8].Parallel findings were achieved by Moledina etal when they compared patients who tested negative with positive patients for COVID-19 who had more AKI (30.6%vs18.2%; absolute risk difference,12.5%[95%CI,10.6%-14.3%]) and dialysis requiring AKI(8.5%vs3.6%) and rates of recovery from AKI were found to be lower (58%vs69.8%). Cause of kidney injury may include a direct effect of COVID- 19 on the kidney or other 19 on the kidney or other unmeasured mediators 9. Kidney injury in patients of Covid-19 is multifactorial and causes range from pre-renalazotemia, ATN due to ischemia or toxins and various types of glomerular involvement.

There is data of autopsy findings in 26 patients by Su H et al who had COVID-19 and AKI. This series has reported that 9 out of these 26 patients had acute tubular injury with some showing frank necrosis. Also, they have noted direct viral infection of kidney as evidenced by ultrastructual and immune histochemistry studies [10]Larsen CP etal reported first kidney biopsy in a living patient who was a black woman with CKD, she developed dialysis requiring AKI and her biopsy showed features of collapsing GN and endothelial tubule reticular inclusions [11] . As per Rossi G M etal and Peleg Yetal the most common outcome on kidney biopsy with COVID-19 has been collapsing glomerulopathy [12,13]. Conversely in clinical practice, ATN seems to be the most common cause

of AKI. All four kidney biopsies showed tubular injury of varying degree, frequently with frank

tubular epitheilial necrosis, variable hyaline droplet changes or lumen filled with cellular debris. All of them were hemodynamically stable. In addition, the severity of Covid-19 infection of all patients was of mild degree with low oxygen requirement. Our findings are consistent with those by Puelles et al as possible mechanisms are intriguing and can be due to renal tropism of SARS-CoV-2 as have been suggested by some studies [14]. Acute tubular necrosis found in all four patients of our series was elicited by ischemia with other possibilities being toxic sepsis associated state, ACE2 inhibition and antibiotics usage. Of four, only one patient had features of FSGS. Another patienthad findings of pauci-immune crescentic GN consistent with her positive ANCA serology; she never suffered symptoms suggestive of vasculitis prodrome before suffering from Covid-19. Her renal parameters, urine output and other systemic symptoms stabilised with

haemodialysis and corticosteroids.

Our findings are consistent with other studies asCOVID-19 affects the kidneys with variety of tubular and glomerular involvement. Acute tubulat necrosis the most shared kidney biopsy feature in all our patients. However, there was no collapsing glomerulopathy in any patient as seen inother case series [12,13,15]. We searched literature about vasculitis in these patients which mentions it as rare and can be a result of "second hit" triggers in patients with predisposition [16]. Although hematuria and proteinuria is present in all, ATN is present in all kidney biopsy findings. Cause of ATN was identifiable in two and in others etiology could not be pointed out. Covid-19 is a inflammatory state associated with cytokine storm. Also, it is known to unmask conditions like ANCA vasculitis. Suggestion of significant viral presence in the kidney tissue by ultrastructural examination was not found in single patient in whom electron microscopy was done, which as per literature may suggest again that direct viral infection is not the main cause of acute kidney injury in those with active Covid-19.

Disclosures:

All authors declare that there is no conflict of interest regarding the publication of this paper.

Statement of Ethics:

The authors have no ethical conflicts to disclose.

Acknowledgements:

Our personal thanks to Dr Sunil Deshpande (Deshpande Pathology Laboratory &
Immuno fluorescence centre, Pune, Maharashtra) for his valuable contribution in kidney biopsy reporting.
Special thanks to Dr Padmaja Motlag, Radiology consultant at Midas Multispeciality Hospital, Nagpur for her assistance in performing kidney biopsies.

References:

1. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19 related death using Open SAFELY. Nature, 2020;584: 430-436.
2. Hirsch Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1): 209-218.
3. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in hospital death of patients with COVID-19. Kid Int. 2020;97 (5): 829-838 .
4. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pnemonia in Wuhan, China. JAMA Intern Med. 2020; 180 (7): 934-943
5. Chen T, Wu D, Chen H, et al Clinical characteristics of 113 deceased patients with coronavirus diease 2019: retrospective study. BMJ,2020; 368m1091
6. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect. 2020;81 (2):16-25.
7. Valeri AM, Robbins-Juarez SY, Stevens JS, et al. Presentation and outcomes of patients with ESKD and COVID-19. J Am SocNephrol. 2020;31(7): 1409-1415.
8. 31. Roshan Kumar Jha, Dhruba Hari Chandi, Dr. Ranjit S. Ambad. ENVIRONMENTAL AND DEMOGRAPHIC FACTOR: ASPECTS ON COVID-19 IN INDIAN POPULATION. Journal of critical reviews. Vol 7, Issue 10, 2020; 1-3.
9. Moledina DG, Simonov M, Yamamoto Y, Alausa J, Arora T, Biswas A, Cantley LG, Ghazi L, Greenberg JH, Hinchcliff M, Huang C, Mansour SG, Martin M, Peixoto A, Schulz W, Subair L, Testani JM, Ugwuowo U, Young P, Wilson FP. The Association of COVID-19 With Acute Kidney Injury Independent of Severity of Illness: A Multicenter Cohort Study. Am J Kidney Dis. 2021 Apr;77(4):490-499.e1. doi:

10.1053/j.ajkd.2020.12.007. Epub 2021 Jan 8. PMID: 33422598; PMCID: PMC7791318.

10. SuH, YangM,Wan C, Yi L-X, Tang F, ZhuH-Y, et al.: Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 98: 219–227, 2020

11. Larsen CP, Bourne TD, Wilson JD, Saqqa O, SharshirMA: Collapsing glomerulopathy in a patient with COVID-19. Kidney Int Rep 5: 935–939, 2020.

12. Rossi GM, Delsante M, Pilato FP, Gnetti L, Gabrielli L, Rossini G, et al.: Kidney biopsy findings in a critically ill COVID-19 patient with dialysis-dependent acute kidney injury: A case against "SARS-CoV-2 nephropathy" [published online ahead of print May 17, 2020]. Kidney Int Rep doi:10.1016/j.ekir.2020.05.005

13. Peleg Y, Kudose S, D'Agati V, Siddall E, Ahmad S, Kisselev S, et al.: Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. Kidney Int Rep 5: 940–945, 2020.

14. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al.: Multiorgan and renal tropism of SARSCoV- 2 [published online ahead of print May 13, 2020]. N Engl J Med doi:10.1056/ NEJMc2011400.

15. Kissling S, Rotman S, Gerber C, Halfon M, Lamoth F, Comte D, et al.: Collapsing glomerulopathy in a COVID-19 patient. Kidney Int 98: 228–231, 2020.

16. Uppal NN, Kello N, Shah HH, Khanin Y, De Oleo IR, Epstein E, Sharma P, Larsen CP, Bijol V, Jhaveri KD. De Novo ANCA-Associated Vasculitis With Glomerulonephritis in COVID-19. Kidney Int Rep. 2020 Nov;5(11):2079-2083. doi: 10.1016/j.ekir.2020.08.012. Epub 2020 Aug 20. PMID: 32839744; PMC