

KIDNEY INJURY FOLLOWING COVID-19: A RETROSPECTIVE STUDY IN A TERTIARY CARE CLINIC

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More than two years have passed since the beginning of the COVID-19 pandemic, with over 500 million people infected by SARS-CoV-2. In this period, thanks to the large amounts of enthusiasm and curiosity the medical community is well known for, an impressive body of evidence and literature regarding COVID-19 has been amassed, looking into every aspect of the disease that even today remains a mystery in a lot of its segments. While there are large amounts of research related to acute COVID-19 and the nuances of its pathophysiology, diagnosis and treatment, a new branch of 'COVID research' is starting to emerge as time passes, i.e., long or post-COVID research, especially following several papers that show that the effects of SARS-CoV-2 on the human body and its organ systems can last for far longer than the acute disease itself. This study assessed the incidence of kidney injury in patients who have previously had COVID-19, confirmed with a positive polymerase chain reaction test. On a modest sample of a little less than 200 patients, we found that around 6% of patients who had mild COVID-19 without the need for hospitalization had some degree of kidney injury that persisted from several weeks to several months. This number tells us that we should monitor COVID-19 patients not only during the active disease phase, but also enable routine checkups several months following the active infection.

Key words: COVID-19, kidney injury, long-COVID, post-COVID, SARS-CoV-2

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INTRODUCTION

Since the beginning of the COVID-19 pandemic, over 500 million people have been infected by SARS-CoV-2 (1). Such a high number of cases was followed by an equally large number of research publications related to COVID-19, with over 250 000 papers written on the topic of SARS-CoV-2 and the disease it causes. While an impressive body of research on acute COVID-19 has amassed and opened the way for new and improved diagnostic and therapeutic modalities and treatment protocols, a new branch of 'COVID research' has recently gained traction, i.e., research on the long-term consequences of COVID-19, the so-called 'post-COVID' or 'long COVID' manifestations. While it is difficult to ascertain that a specific symptom or disease process is a direct consequence of a previous SARS-CoV-2 infection, clinicians are eager for research evidence they can refer to while caring for patients following acute COVID-19. We have previously studied 'new onset' arterial hypertension follow-

ing mild COVID-19 (2) and found sharing our experience as a tertiary care nephrology clinic potentially useful. The aim of this paper, therefore is to describe our patient population with 'new onset' kidney injury following mild COVID-19 and compare them to patients with other 'post-COVID' manifestations.

MATERIAL AND METHODS

This was a retrospective study done in a tertiary care center, studying post-COVID symptomatology in a population of patients cared for in the Nephrology, Hypertension and General Internal Medicine clinics. Patient data were obtained from the Hospital Informatics System and entered into a database. Data were collected from the history and clinical examination notes and laboratory results. The inclusion criteria were a chief complaint of a novel symptom manifested following a mild case of COVID-19 confirmed by a positive polymerase chain reaction (PCR) for SARS-

CoV-2. Patients without a positive SARS-CoV-2 PCR test in the past medical data and patients with incomplete medical history or laboratory test results were excluded from the study. The data collected covered a one-year period spanning from January 2021 to February 2022. Patients were divided into two groups of those with kidney injury and those with other post-COVID manifestations. Statistical analysis was performed in the open-source JASP statistics program.

RESULTS

The study included 197 patients, 106 female and 91 male. The median patient age was 57 years. The median time elapsed from a positive PCR test for SARS-CoV-2 onset of symptoms was 2 months. There were 12 patients in the kidney injury group and 185 patients in the group with other post-COVID manifestations. Statistically significant differences in laboratory and clinical findings between the two groups are displayed in Table 1. There were no statistically significant differences in patient age, body mass index (BMI), systolic blood pressure, AST, ALT, GGT, ALP, total serum bilirubin or time from positive SARS-CoV-2 PCR test to symptom onset. There were differences in serum sodium and calcium designated as statistically significant, but these were most likely the result of the kidney injury group being much smaller (n=12) and therefore will not be considered significant in further discussion. Primary diseases in the kidney injury group patients are listed in Table 2. While some of the patients had a primary disease that put them at a higher risk of developing renal function decline (e.g., arterial hypertension, diabetes mellitus), most of the primary conditions were unrelated to kidney injury in their pathophysiology.

Table 1. Statistically significant differences between kidney injury and non-kidney injury groups of patients.

	Kidney injury group	Non-kidney injury group	p value
Number of patients	12 (6.09%)	185 (93.91%)	-
Serum creatinine (µmol/L)	113	74.5	<0.001
C-reactive protein (mg/L)	76.4	32.6	0.033
Red blood cell count (cells/L)	4.19 * 10 ⁹	4.71 * 10 ⁹	<0.001
Prothrombin time (1)	0.89	0.92	<0.001
Diastolic blood pressure (mm Hg)	79	84	0.033

Table 2. Primary diseases in the kidney injury group patients.

Primary disease in kidney injury group patients	Number of patients
Arterial hypertension (OSA syndrome)	1
Hodgkin lymphoma	1
Crohn's disease	1
Type 2 diabetes mellitus	1
Pregnancy	1
Multiple myeloma	1
Prostate cancer	1
Post operation – uterine carcinoma	2
Previously healthy	3

DISCUSSION

There are several mechanisms proposed for SARS-CoV-2 causing kidney injury, including direct viral damage, ACE-2 receptor-mediated damage and immune-mediated damage. Support for the direct viral damage comes from the finding that SARS-CoV-2 nucleocapsid protein (NP) has been recovered from the renal tissue of patients who died from COVID-19 (3). The ACE-2 receptor-mediated damage theory is based on the finding that ACE-2 receptor expression in the kidneys is at least equal to its expression in lung tissue (4). Finally, autopsies of patients who died from COVID-19 showed deposition of complement 5b-9 and CD68+ macrophages in renal tissue (3).

The incidence of kidney injury during or following mild COVID-19 has a wide margin of reporting, spanning from 3% to 15% of patients (5,6), but most of these studies followed hospitalized patients, where factors other than COVID-19 itself, such as dehydration, hypotension, concurrent bacterial infection from indwelling urinary catheters, etc. can precipitate kidney injury. This study, including only non-hospitalized patients cared for in the nephrology clinic, determined an incidence of kidney injury following mild COVID-19 of 6.09%. The importance of a study done on such a population lies exactly in the fact that most of the patients followed up and monitored for post-COVID manifestations are the ones that were hospitalized for COVID-19, while new-onset renal pathology in the non-hospitalized population that had the mild form of COVID-19 can often go unnoticed. This fact is problematic when taking into account the fact that more than 1 per 20 patients will suffer some degree of lasting kidney damage. The importance of this

finding is further confirmed by a study (7) reviewing renal outcomes in patients following acute COVID-19, which shows that non-hospitalized patients who had COVID-19 display an excess estimated glomerular filtration rate (eGFR) decline of 3.26 mL/min/1.73 m² per year as compared to non-infected controls.

There is increasing awareness of the negative influence of post-COVID symptoms on population health, especially following the publication of new data on the topic. A retrospective analysis of 193 113 patients aged 18-65 years published by Daugherty *et al.* shows that 14% of the analyzed population had a new clinical condition that required medical management following COVID-19 (8). They found more than 50 clinical manifestations of post-COVID, including but not limited to chronic respiratory failure, hypercoagulation states, cardiac arrhythmias, myocarditis, peripheral neuropathy, etc. A review of the impact of post-COVID on healthcare economics demonstrated that over 30% of the total disease burden of COVID-19 was not due to mortality but due to post-COVID-induced disability (9). While there are no clear guidelines or markers used to follow up patients with renal function decrease following COVID-19, a novel biomarker of chronic kidney disease progression has been recently introduced, i.e., urinary dickkopf-3 (uDKK3). A study has shown that it remains elevated in cases of eGFR decline following COVID-19 even after 6 months (10) and could therefore serve as a valuable tool in distinguishing renal damage caused by COVID-19 from renal damage caused by other etiopathogenetic factors.

CONCLUSION

In this retrospective study of patients with kidney injury following mild COVID-19, we showed that there was a relatively high incidence of renal damage in the study population (6% or approximately 1 per 16 patients). Since there are no major biochemical or clinical markers differentiating patients with kidney injury from patients without kidney injury (except for creatinine), we recommend providing every patient who had COVID-19 with a follow-up examination 3 months from the active infection (11), which includes measuring blood pressure and cardiac pulse and determining serum concentrations of creatinine and C-reactive protein in order to screen for new-onset arterial hypertension [which is also a common occurrence in this patient population with an incidence of approximately 15% (2)] and new-onset kidney injury.

R E F E R E N C E S

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020; 20(5): 533-4. doi: 10.1016/S1473-3099(20)30120-1.
2. Delalić Đ, Jug J, Prkačin I. Arterial hypertension following COVID-19: a retrospective study of patients in a Central European tertiary care center. *Acta Clin Croat* 2022; 61 (Suppl 1): 23-6. doi: 10.20471/acc.2022.61.s1.03.
3. Diao B, Feng Z, Wang C *et al.* Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *Nat Commun* 2021; 12(1): 2506. doi: 10.1038/s41467-021-22781-1.
4. Pan XW, Xu D, Zhang H *et al.* Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. *Intensive Care Med* 2020; 46(6): 1114-6. doi: 10.1007/s00134-020-06026-1.
5. Cheng Y, Luo R, Wang K *et al.* Kidney disease is associated with in-hospital death of COVID-19 patients. *Kidney Int* 2020; 97(5): 829-38. doi: 10.1016/j.kint.2020.03.005.
6. Zhou F, Yu T, Du R *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395(10229): 1054-62. doi: 10.1016/S0140-6736(20)30566-3.
7. Bowe B, Xie Y, Xu E, Al-Aly Z. Kidney outcomes in long COVID. *J Am Soc Nephrol* 2021; 32(11): 2851-62. doi: 10.1681/ASN.2021060734.
8. Daugherty SE, Guo Y, Heath K *et al.* Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* 2021; 373: 1098. doi: 10.1136/bmj.n1098.
9. Raman B, Cassar MP, Tunnicliffe EM *et al.* Living with COVID-19 second review. *Natl Inst Health Res* [cited Oct 18 2022]. Available from: <https://evidence.nihr.ac.uk/themedreview/living-with-covid19-second-review/>. doi:10.3310/theme-dreview_45225
10. Husain-Syed F, Villa G, Wilhelm J *et al.* Renal markers for monitoring acute kidney injury transition to chronic kidney disease after COVID-19. *Nephrol Dial Transplant* 2021; 36(11): 2143-7. doi: 10.1093/ndt/gfab235.
11. Prkačin I, Mileta D, Delalić Đ. Zbrinjavanje bolesnika s komplikacijama prije i nakon bolesti COVID-19. In: Kardum Paro MM, editor. *Laboratorijska dijagnostika u epidemiji bolesti COVID-19 prouzročenoj virusom SARS-CoV-2. Priručnik za trajno usavršavanje*. Zagreb: Medicinska naklada, 2021; 69-76; ISBN 978-953-7468-53-8. (in Croatian)

S A Ž E T A K

OŠTEĆENJE BUBREGA NAKON COVID-19: RETROSPEKTIVNA STUDIJA U TERCIJARNOM CENTRU

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Više od dvije godine je prošlo od početka pandemije COVID-19 s preko 500 milijuna ljudi zaraženih SARS-CoV-2. U tom se razdoblju, zahvaljujući velikim količinama entuzijazma i znatiželje po kojima je medicinska zajednica poznata, nakupila impresivna količina znanstvenih dokaza i literaturnih podataka vezanih uz COVID-19, koji istražuju svaki aspekt bolesti koja i danas ostaje u svojim brojnim dijelovima zagonetna. I dok postoji velik broj istraživanja povezanih s akutnim COVID-19 i njegovom patologijom, dijagnostikom i liječenjem, s prolaskom se vremena pojavljuje nova grana "COVID istraživanja", istraživanja o *post*-COVID ili *long* COVID-u, poglavito nakon objave nekoliko kvalitetnih radova koji pokazuju da utjecaj na ljudsko tijelo i organske sustave može trajati značajno dulje od same akutne bolesti. Ovaj rad istražuje pojavnost bubrežne ozljede kod pacijenata koji su prethodno imali COVID-19 potvrđen pozitivnim PCR testom. Na skromnom uzorku od malo manje od 200 pacijenata pronašli smo da oko 6 % pacijenata koji su imali blagi oblik COVID-19 bez potrebe za hospitalizacijom ima određen stupanj bubrežne ozljede koja je potrajala od nekoliko tjedana do nekoliko mjeseci. Ovaj nam broj ukazuje na to da bismo trebali promatrati pacijente oboljele od COVID-19 ne samo tijekom faze aktivne bolesti, nego im omogućiti pristup rutinskim kontrolnim pregledima nekoliko mjeseci nakon aktivne infekcije.

Ključne riječi: oštećenje bubrega, COVID-19, *long*-COVID, *post*-COVID, SARS-CoV-2