Annals of Medicine and Surgery 64 (2021) 102223

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Damage to the waterworks: COVID-19 and the kidneys

The coronavirus disease 2019 (COVID-19) continues to elicit turmoil globally, culminating in a myriad of challenges for the general public, physicians, and healthcare systems alike. Although it primarily affects the respiratory system, there are several extrapulmonary ramifications, which are being fervently explored by researchers around the world. A growing amount of literature has established several extrapulmonary sequelae, including cardiovascular, hepatic, gastrointestinal, neurological and—more importantly—nephrological complications. Whether it is the occurrence of acute kidney injury in COVID-19 patients, or the effects of the virus in patients with chronic kidney disease and kidney transplant recipients, the pathophysiology of nephrological involvement remains esoteric despite its paramount significance. In order to devise efficacious management protocols, it is crucial to unravel and shed light on the inexplicable pathophysiological basis underlying COVID-19 induced kidney injury.

It is important to note that incidence rates for acute kidney injury (AKI) have evolved throughout the pandemic. During the initial stages of the pandemic, the incidence of AKI was noted to be as low as 4.9% in hospitalised COVID-19 patients [1]. However, as the pandemic progressed, further reports that emerged from China estimated the incidence of AKI to be between 1% and 46%, whilst those studies outside of China insinuated incidence levels hovering around 15% [2]. These estimations are comparable with those of severe acute respiratory syndrome (SARS) [3]. The two main causes of AKI amongst COVID-19 patients are hypovolemia and dehydration, with AKI portending worse outcomes with respect to pulmonary and renal damage, as well as in-hospital mortality [4,5]. Interestingly, patients who developed AKI while hospitalised with COVID-19 are postulated to be at a higher risk of mortality than those without, with stages 1, 2 and 3 AKI all associated with higher mortality (hazard ratios: 3.51 to 9.81) [4]. Variance in incidence of AKI, transplants (kidney replacement therapy) and mortality is assumed to be down to numerous comorbidities, ranging from race to education [2,6].

Renal involvement in COVID-19 is thought to be multifactorial; however, its exact mechanisms still remain enigmatic. Multiple predisposing factors such as cardiovascular comorbidities, nephrotoxins, and hypovolemia also play a role as possible contributors to involvement of the kidneys [7]. There is mounting evidence substantiating the role of SARS-CoV-2 in causing direct kidney injury [7]. Post-mortem studies using light microscopy have shown acute tubular injury amongst those that died from COVID-19 induced AKI [2,8]. Furthermore, electron microscopy has found viral particles in the epithelium as well as podocytes [8,9]. Specific mechanisms that have been proposed include direct injury via angiotensin-converting enzyme 2 (ACE2) receptors, an imbalance of the renin-angiotensin-aldosterone system (RAAS), a rise in cytokines, and microvascular thrombosis [10]. ACE2 receptors have been found to be a major binding agent for SARS-CoV-2 in the lungs, leading to acute lung injury [6]. Expression of ACE2 RNA is nearly a hundred times higher in the kidneys as opposed to the lungs, further highlighting the susceptibility of the kidneys to injury [10,12]. SARS-CoV-2 can infect cells in kidneys through the ACE2 receptors, thereby leading to mitochondrial failure, collapsing glomerulopathy, protein leakage, and acute tubular necrosis [7].

SARS-CoV-2 can also lead to an imbalance within the RAAS system. When SARS-CoV-2 binds to ACE2 receptors, membrane-bound ACE2 receptors are downregulated, culminating in an accumulation of angiotensin II. This results in an overactivation of RAAS, eventually resulting in vasoconstriction, inflammation, and fibrosis [10]. It has thus been suggested that RAAS inhibitors, which include angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), might indeed be effective agents in combating COVID-19. However, ACE inhibitors and ARBs may also increase the expression ACE2 receptors, leading to adverse outcomes [10,11]. COVID-19 induced cytokine storm has also been implicated in AKI witnessed in patients afflicted with SARS-CoV-2 [7,8]. Evidence suggests that patients with COVID-19 can have an increased number of inflammatory cytokines, which can in turn induce endothelial and tubular. In particular, IL-6 can be particularly menacing and may play a role in ischemic AKI, sepsis-induced AKI, and nephrotoxin-induced AKI. Additionally, due to the widespread endothelial dysfunction that ensues in the context of a severe COVID-19 infection, fibrin thrombi can deposit in the glomerular loops, leading to a failure in coagulation and haemostasis [10]. This can be further exacerbated in patients with inherited or acquired prothrombotic conditions [8].

Chronic kidney disease (CKD) is described as a structural or functional abnormality of kidneys lasting more than 3 months and boasts an estimated global prevalence of 13.4% (95%CI: 11.7%–15.1%) [13,14]. Pertinently, a recent meta-analysis found that there is a noteworthy relationship of CKD with severe COVID-19 infection [OR 3.03, 95% CI: 1.09–8.47) [15]. Therefore, CKD is conjectured to be an important prognosticator of mortality in hospitalised COVID-19 patients [16]. A recent study from the US concluded that patients with CKD had an increased risk of mortality (RR: 2.51 [1.82–3.47]) whilst a study from Italy reported a mortality rate of 88.2% amongst infected patients with underlying CKD [17]. According to another mortality analysis, COVID-19 patients with CKD are at a higher risk of ICU admission and in-hospital mortality, with rates of 39.4% and 28.4%, respectively, in contrast to patients without pre-existing CKD (8.0% and 4%, respectively) [18].

Kidney transplant recipients with chronic immunosuppression and coexisting conditions are more likely to develop critical COVID-19 disease, which increases the likelihood of hospitalization and mortality. A case series divulged a 32% mortality in the aforesaid patient group [19]. According to another study, infected kidney transplant patients had

https://doi.org/10.1016/j.amsu.2021.102223
Received 5 March 2021; Accepted 10 March 2021
Available online 15 March 2021

lower CD3, CD4, and CD8 cell counts, and experienced a faster clinical deterioration than infected patients without CKD [19]. The management of this patient population is still a medical conundrum, since there is no established consensus regarding the way to modulate immunosuppression in patients undergoing kidney transplantation. In this context, immunosuppression might thwart a coordinated anti-virus T-cell response, but it may also inhibit the body's inflammatory response, which contributes to COVID-related mortality [20].

While the pulmonary manifestations of COVID-19 are well-documented, the mechanisms underlying COVID-19 induced renal damage still remain elusive. As the pandemic continues to take its toll, physicians must remain cognisant of these emerging extrapulmonary adverse outcomes. Over the coming months, it would be intriguing to note the percentage of patients with underlying CKD who eventually develop end-stage renal disease in the context of a severe COVID-19 infection. Equally important, it might be the case that, akin to HIV, COVID-19 might employ the renal epithelial cells as a potential reservoir, a notion that can be extensively researched upon.

Ethical approval

NA.

Sources of funding

NA.

Author contribution

AH, TA, ARN: conceived the idea, designed the study, and drafted the manuscript.

JCC, AA, TA: conducted literature search and created the illustrations.

MAN, GG, TA: revised the final version of the manuscript critically and gave the final approval.

Registration of research studies

Name of the registry: NA.

Unique Identifying number or registration ID: NA.

Hyperlink to your specific registration (must be publicly accessible and will be checked): NA.

Guarantor

Talal Almas.
RCSI University of Medicine and Health Sciences.
123 St. Stephen's Green.
Dublin 2, Ireland.
Talalalmas.almas@gmail.com.
+353834212442.

Consent

NA.

Declaration of competing interest

NA.

References

[1] G. Xiao, H. Hu, F. Wu, T. Sha, Q. Huang, H. Li, et al., Acute Kidney Injury in Patients Hospitalized with COVID-19 in Wuhan, China: A Single-Center Retrospective Observational Study, medRxiv [Internet], 2020 Jan 1, 2020.04.06.20055194. Available from: http://medrxiv.org/content/early/2020/04/08/2020.04.06.20055194.abstract.

[2] S.S. Farouk, E. Fiaccadori, P. Cravedi, K.N. Campbell, COVID-19 and the kidney: what we think we know so far and what we don't, 2020/07/20, J. Nephrol. 33 (6) (2020 Dec), 1213–8. Available from: https://pubmed.ncbi.nlm.nih.gov/32691342.

[3] I. Gagliardi, G. Patella, A. Michael, R. Serra, M. Provenzano, M. Andreucci, COVID-19 and the kidney: from epidemiology to clinical practice, J. Clin. Med. 9 (8) (2020 Aug 4) 2506. Available from: https://pubmed.ncbi.nlm.nih.gov/32759645.

[4] Y. Cheng, R. Luo, K. Wang, M. Zhang, Z. Wang, L. Dong, et al., Kidney disease is associated with in-hospital death of patients with COVID-19, Kidney Int. 97 (5) (2020 May) 829–838.

[5] B. Tarragón, M. Valdenebro, M.L. Serrano, A. Maroto, M.R. Llópez-Carratalá, A. Ramos, et al., Acute kidney failure in patients admitted due to COVID-19, Nefrologia 41 (1) (2021) 34–40.

[6] E. Akalin, Y. Azzi, R. Bartash, H. Seethamraju, M. Parides, V. Hemmige, et al., Covid-19 and kidney transplantation, N. Engl. J. Med. 382 (25) (2020 Apr 24) 2475–2477, https://doi.org/10.1056/NEJMc2011117. Available from:.

[7] C. Ronco, T. Reis, F. Husain-Syed, Management of acute kidney injury in patients with COVID-19, Lancet Respir. Med. 8 (7) (2020 Jul) 738–742, https://doi.org/10.1016/S2213-2600(20)30229-0. Epub 2020 May 14. PMID: 32416769; PMCID: PMC7255232.

[8] M.K. Nadim, L.G. Forni, R.L. Mehta, M.J. Connor Jr., K.D. Liu, M. Ostermann, T. Rimmelé, A. Zarbock, S. Bell, A. Bihorac, V. Cantaluppi, E. Hoste, F. Husain-Syed, M.J. Germain, S.L. Goldstein, S. Gupta, M. Joannidis, K. Kashani, J.L. Koyner, M. Legrand, N. Lumlertgul, S. Mohan, N. Pannu, Z. Peng, X.L. Perez-Fernandez, P. Pickkers, J. Prowle, T. Reis, N. Srisawat, A. Tolwani, A. Vijayan, G. Villa, L. Yang, C. Ronco, J.A. Kellum, COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup, Nat. Rev. Nephrol. 16 (12) (2020 Dec) 747–764, https://doi.org/10.1038/s41581-020-00356-5. Epub 2020 Oct 15. Erratum in: Nat Rev Nephrol. 2020 Nov 2;: PMID: 33060844; PMCID: PMC7561246.

[9] P. Sharma, N.N. Uppal, R. Wanchoo, H.H. Shah, Y. Yang, R. Parikh, Y. Khanin, V. Madireddy, C.P. Larsen, K.D. Jhaveri, V. Bijol, Northwell Nephrology COVID-19 Research Consortium, COVID-19-Associated kidney injury: a case series of kidney biopsy findings, J. Am. Soc. Nephrol. 31 (9) (2020 Sep) 1948–1958, https://doi.org/10.1681/ASN.2020050699. Epub 2020 Jul 13. PMID: 32660970; PMCID: PMC7461689.

[10] P. Gabarre, G. Dumas, T. Dupont, M. Darmon, E. Azoulay, L. Zafrani, Acute kidney injury in critically ill patients with COVID-19, Intensive Care Med. 46 (7) (2020 Jul) 1339–1348, https://doi.org/10.1007/s00134-020-06153-9. Epub 2020 Jun 12. PMID: 32533197; PMCID: PMC7290076.

[11] H. Kai, M. Kai, Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19, Hypertens. Res. 43 (7) (2020 Jul) 648–654, https://doi.org/10.1038/s41440-020-0455-8. Epub 2020 Apr 27. PMID: 32341442; PMCID: PMC7184165.

[12] J.A. Kellum, J.W.O. van Till, G. Mulligan, Targeting acute kidney injury in COVID-19, Nephrol. Dial. Transplant. 35 (10) (2020 Oct 1) 1652–1662, https://doi.org/10.1093/ndt/gfaa231. PMID: 33022712; PMCID: PMC7665651.

[13] Chapter 1: definition and classification of CKD, 2013 Jan, Kidney Int. Suppl. 3 (1) (2011) 19–62, https://doi.org/10.1038/kisup.2012.64. PMID: 25018975; PMCID: PMC4089693.

[14] J.-C. Lv, L.-X. Zhang, Prevalence and disease burden of chronic kidney disease, Adv. Exp. Med. Biol. 1165 (2019) 3–15.

[15] B.M. Henry, G. Lippi, Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection, 2020/03/28, Int. Urol. Nephrol. 52 (6) (2020 Jun), 1193–4. Available from: https://pubmed.ncbi.nlm.nih.gov/32222883.

[16] T. Yamada, T. Mikami, N. Chopra, H. Miyashita, S. Chernyavsky, S. Miyashita, Patients with chronic kidney disease have a poorer prognosis of coronavirus disease 2019 (COVID-19): an experience in New York City, 2020/05/26, Int. Urol. Nephrol. 52 (7) (2020 Jul), 1405–6. Available from: https://pubmed.ncbi.nlm.nih.gov/32458212.

[17] F. Malberti, P. Pecchini, G. Marchi, M. Foramitti, When a nephrology ward becomes a COVID-19 ward: the Cremona experience, J. Nephrol. 33 (4) (2020 Aug) 625–628. Available from: https://pubmed.ncbi.nlm.nih.gov/32430898.

[18] S. Ozturk, K. Turgutalp, M. Arici, A.R. Odabas, M.R. Altiparmak, Z. Aydin, E. Cebeci, T. Basturk, Z. Soypacaci, G. Sahin, T. Elif Ozler, E. Kara, H. Dheir, N. Eren, G. Suleymanlar, M. Islam, M.B. Ogutmen, E. Sengul, Y. Ayar, M. E. Dolarslan, S. Bakirdogen, S. Safak, O. Gungor, I. Sahin, I.B. Mentese, O. Merhametsiz, E.G. Oguz, D.G. Genek, N. Alpay, N. Aktas, M. Duranay, S. Alagoz, H. Colak, Z. Adibelli, I. Pembegul, E. Hur, A. Azak, D.G. Taymez, E. Tatar, R. Kazancioglu, A. Oruc, E. Yuksel, E. Onan, K. Turkmen, N.B. Hasbal, A. Gurel, B. Yelken, T. Sahutoglu, M. Gok, N. Seyahi, M. Sevinc, S. Ozkurt, S. Sipahi, S. G. Bek, F. Bora, B. Demirelli, O.A. Oto, O. Altunoren, S.Z. Tuglular, M.E. Demir, M. D. Ayli, B. Huddam, M. Tanrisev, I. Bozaci, M. Gursu, B. Bakar, B. Tokgoz, H. Z. Tonbul, A. Yildiz, S. Sezer, K. Ates, Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey, Nephrol. Dial. Transplant. 35 (12) (2020 Dec 4) 2083–2095, https://doi.org/10.1093/ndt/gfaa271. PMID: 33275763; PMCID: PMC7716804. Available from: https://pubmed.ncbi.nlm.nih.gov/33275763/.

[19] E. Akalin, Y. Azzi, R. Bartash, H. Seethamraju, M. Parides, V. Hemmige, M. Ross, S. Forest, Y.D. Goldstein, M. Ajaimy, L. Liriano-Ward, C. Pynadath, P. Loarte-Campos, P.B. Nandigam, J. Graham, M. Le, J. Rocca, M. Kinkhabwala, Covid-19 and kidney transplantation, N. Engl. J. Med. 382 (25) (2020 Jun 18) 2475–2477, https://doi.org/10.1056/NEJMc2011117. Epub 2020 Apr 24. PMID: 32329975; PMCID: PMC7200055.

[20] P. Cravedi, S.S. Mothi, Y. Azzi, M. Haverly, S.S. Farouk, M.J. Pérez-Sáez, M. D. Redondo-Pachón, B. Murphy, S. Florman, L.G. Cyrino, M. Grafals,

S. Venkataraman, X.S. Cheng, A.X. Wang, G. Zaza, A. Ranghino, L. Furian, J. Manrique, U. Maggiore, I. Gandolfini, N. Agrawal, H. Patel, E. Akalin, L.V. Riella, COVID-19 and kidney transplantation: results from the TANGO international transplant consortium, Am. J. Transplant. 20 (11) (2020 Nov) 3140–3148, https://doi.org/10.1111/ajt.16185. Epub 2020 Aug 4. PMID: 32649791; PMCID: PMC7405285.

Abdul Haadi, Talal Almas*, Abdur Rahman Nabeel, Josiah CY. Chan, Abdulla Hussain Al-Awaid, Muhammad Ali Niaz

RCSI University of Medicine and Health Sciences, Dublin, Ireland

Gabriel Gurmail-Kaufmann
University College London, United Kingdom

* Corresponding author. RCSI University of Medicine and Health Sciences, 123 St. Stephen's Green, Dublin 2, Ireland.
E-mail address: Talalalmas.almas@gmail.com (T. Almas).