Int J Med Rev 2022 June;9(2): 263-267

doi 10.30491/IJMR.2022.268732.1176

INTERNATIONAL JOURNAL OF MEDICAL REVIEWS

Narrative Review

Effects of the Coronavirus Disease-2019 (COVID-19) on Kidney Functions

Khojasteh Malekmohammad [1], Firouzeh Gholampour [1*]

[1] Department of Biology, School of Science, Shiraz University, Shiraz, Iran

*** Corresponding Author:** Firouzeh Gholampour, Department of Biology, School of Science, Shiraz University, Shiraz, Iran. E-mail: gholampour@shirazu.ac.ir

Received January 15, 2021; **Accepted** April 4, 2022; **Online Published** June 5, 2022

Abstract

Coronavirus disease 2019 (COVID-19) is a contagious and lethal infectious disease with a potential threat to global health security. Kidney is a multi-organ that has been affected by COVID-19. Angiotensin-Converting Enzyme 2 (ACE2) expression in the different cell populations of kidney including podocytes, proximal tubular cells and so on shows a possible association between renal parenchymal cells involvement and direct Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) invasion to kidney parenchyma at an early stage of disease. Considering the importance of the kidney, this review article highlights the recent findings about the influence of COVID-19 on kidney functions.

The main manifestations of the renal complications include proteinuria, elevated plasma creatinine and blood urea nitrogen, hematuria and less frequently, acute tubular injury (ATI) and Acute Kidney Injury (AKI), direct infection of tubular epithelial cells and podocytes, reduced density of kidney, inflammation and edema of the renal parenchyma. The potential pathogenic mechanisms of kidney involvement in COVID-19 patients include direct infection of tubules, dehydration, cytokine-induced systemic inflammatory immune response, organ crosstalk, and drug-induced cytotoxicity.

In accordance to clinical manifestations of COVID-19 and the prevalence rate of SARS-CoV-2 in public health, we need to pay more attention to the regularly monitoring of renal function and treatment strategy against the infection of SARSCoV-2 to the renal tissue.

Keywords: Angiotensin-Converting Enzyme 2, ACE-2, COVID-19, Renal Function, SARS-CoV-2

Introduction

Coronavirus Disease 2019 (COVID-19), a disease caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a contagious and lethal infectious disease with a potential threat to global health security.[1] On March 11, 2020, the World Health Organization (WHO) called the name of SARS-CoV-2-related disease ‘‘COVID-19’’.[2] On electron microscopy, this novel virus has solar corona appearance (corona in Latin means crown) due to the presence of club-shaped spikes protein projections on its surface.[3,4]

Although the respiratory system is the main organ system involved in the manifestation of COVID-19, but SARS-CoV-2 invades other organs including gastrointestinal tract, heart, renal and nervous systems and liver. These organs have SARS-CoV-2 receptor.[5,6]

Angiotensin-Converting Enzyme 2 (ACE2), a membrane exopeptidase, is a functional receptor for SARS-CoV-2 and a crucial counter-regulatory enzyme within the Renin–Angiotensin System (RAS).[7,8] It is expressed by type 2 alveolar epithelial cells in the lungs and by cells in other extrapulmonary tissues, including the heart, kidney, gastrointestinal system, duodenum, small intestine, nervous system, artery smooth muscle cells, spermatogonia, leydig cells, sertoli cells, rectal epithelial cells and vascular endothelia.[9-14]

The expression of ACE2 gene in the kidney tissue was 100-fold higher than that in the lung tissue.[15,16] ACE2 expression in different cell populations of the kidney including podocytes, brush border of proximal tubular cells and the endothelium shows a possible association between renal parenchymal cells involvement and direct SARS-CoV-2 invasion to kidney parenchyma at an early stage.[17,18]

The most important physiological roles of ACE2 in the kidney are: conversion of angiotensin II to angiotensin 1-7, degradation of angiotensin II, nephrin upregulation and preventing the loss of proteins in

podocytes, sodium balance and natriuresis in the brush border of proximal tubular cells.[19]

SARS-CoV-2 Entry Pathways in Renal Tissue

1. The binding of the SARS-CoV-2, spike protein to ACE2 in the lung. Transmembrane serine proteases (TMPRSSs) family especially TMPRSS2 and TMPRSS11D are necessary for spike glycoprotein priming. TMPRSSs facilitate cell membrane fusion and entry of the virus into cells, viral replication and cell-to-cell transmission through activation and cleavage of SARS-CoV-2 S protein.[20-24] Also, the co-expression of ACE2 and TMPRSSs in podocytes, proximal convoluted and straight tubules, collecting duct and distal tubule cells is a key determinant for the entry of SARS-CoV-2 into host cells.[22]

2. After lung infection, the virus circulates in the blood to reach kidney through systemic circulation and then enters in the arterioles and glomerular capillaries. SARS-CoV-2 causes infection of glomerular endothelial cells.

3. Active crawling of SARS-CoV-2 particles through glomerular filtration barrier due to their large size.[25]

4. Reaching the virus to Bowman's space and infecting the podocytes and collapsing focal segmental glomerulopathy.[26]

5. Direct infection of proximal tubular epithelium and even distal tubules.[22, 27-28]

Recently a new route has been detected for SARS-CoV-2 entering target cells. SARS-CoV-2 invades host cells via CD147-spike protein.[29] In fact, CD147, a transmembrane glycoprotein, is expressed only in the basolateral side of tubular epithelial cells (TECs).[30]

Despite intense research efforts on the effects of SARS-CoV-2 and COVID-19 on respiratory and immune systems, there is limited information on renal function and pathogenesis of kidney damage in patients with COVID-19. Hence, increasing awareness about the mechanistic impacts of the virus on kidney functions as a vital organ and preventive strategies among people can be helpful for timely diseases control and improving therapeutic options. So consequently, this study aims to comprehensively review the SARS-CoV-2 mechanism of action in kidney and effects of SARS-CoV-2 on renal function.

SARS-CoV-2 Infection and Renal Injury

COVID-19 is a major problem for nephrologists, because recent studies indicated the existence of viral RNA in urine samples and accumulation of SARS-CoV-2 antigens in kidney tubules. It protects the evidence of viral tropism for specific renal cells.[31-33] Patients with various chronic diseases, like hypertension, diabetes or heart disease are high-risk groups than the general population.[34,35]

Based on clinical and laboratory findings in COVID-19 patients, renal disturbances by COVID-19 consisted of proteinuria, albuminuria, hematuria, elevation in blood urea nitrogen and serum creatinine with glomerular filtration rate <60 ml/min per 1.73 m^2, inflammation and interstitial edema.[15,36-37] AKI is a severe symptom of the SARS-CoV-2 due to acute tubular necrosis resulted from direct infection, sepsis, hydration, cytokine storm syndrome, rhabdomyolysis and hypoxia.[4,38] SARS-CoV-2 impacts on podocytes through inducing autophagy, functional decrease of ACE-2, decrease in nephrin levels and increase of proteinuria.[22,39]

The histopathological analyses of SARS-CoV-2 has an effect on renal tissue demonstrate severe acute tubular necrosis, luminal brush border sloughing, vacuole degeneration, severe infiltration of lymphocytes in the tubulointerstitium, higher leukocyte count, collapsing focal segmental glomerulopathy, and dilated capillary vessels in the glomeruli of COVID-19 patients.[15,31]

Computerized Tomography scan (CT scan) of the kidneys reveals reduced density of kidney, suggestive of swelling, inflammation and edema of the renal parenchyma.[36,40]

The Pathophysiological Mechanisms of Renal Involvement by COVID-19

1. Direct infection of renal tubules (distal convoluted tubules and proximal straight tubular cells) and interstitium or glomeruli.[31,32] Figure 1 depicts patho-physiological mechanisms of kidney injury by SARS-CoV-2

2. Immune system activation and dysregulation

Cytokine Release Syndrome (CRS), also termed 'cytokine storm', is a systemic inflammatory immune response.[41,42] Cytokine overproduction and uncontrolled release of plasma pro-inflammatory cytokines include interferon alpha (IFN-α), interferon beta (IFN-β), interferon gamma (IFN-γ), interleukin-1 (IL-1), interleukin (IL-2), interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 10 (IL-10), interleukin 12 (IL-12),

interleukin 18 (IL-18), interleukin 33 (IL-33), Granulocyte colony-stimulating factor (G-CSF or GCSF), Monocyte Chemotactic Protein 1 (MCP-1), tumor necrosis factor alpha (TNF-α), Transforming Growth Factor beta (TGF- β) and chemokines, called cytokine storm.[43] Pro-inflammatory IL-6 is the most important causative cytokine in CRS pathophysiology.[42] IFN-γ secretion activates immune cells including macrophages.[42] Renal tubular and interstitial damages occur in COVID-19 patients through infiltrating renal parenchyma by inflammatory cells like CD68+ macrophages, CD4+ T cells, and CD56+ natural killer cells due to promotion of fibrosis, induction of epithelial cell apoptosis, membrane-attack complex (MAC) or C5b-9 complexes expression and deposition on tubules or glomeruli.[31,35]

CRS related to sepsis or rhabdomyolysis leads to indirect toxic cellular and tubular damages, hypoxia, killing large numbers of normal human lung and kidney cells, shock or even acute renal dysfunction and AKI.[15,36] Sepsis is an intense host systemic inflammatory response to SARS-CoV-2 infection. It is one of the principal mechanisms of kidney damage. Cytokine storm cascade and unregulated pro-inflammatory mediators are the principal causes of sepsis.[44] Hypoxia, shock and insufficient blood flow from afferent arterioles as a result of cytokines release can cause AKI. Low-oxygen delivery to renal tissue in the setting of this disease may lead to ischemic damage of the kidney.[15]

3. Cytopathic action, virus entry into the renal tubular epithelial cells through binding to ACE2 receptors existed on the renal epithelial cell surface.[32,34] SARS-CoV-2 invades human podocytes to cause the virus-induced cytopathic effect.[22]

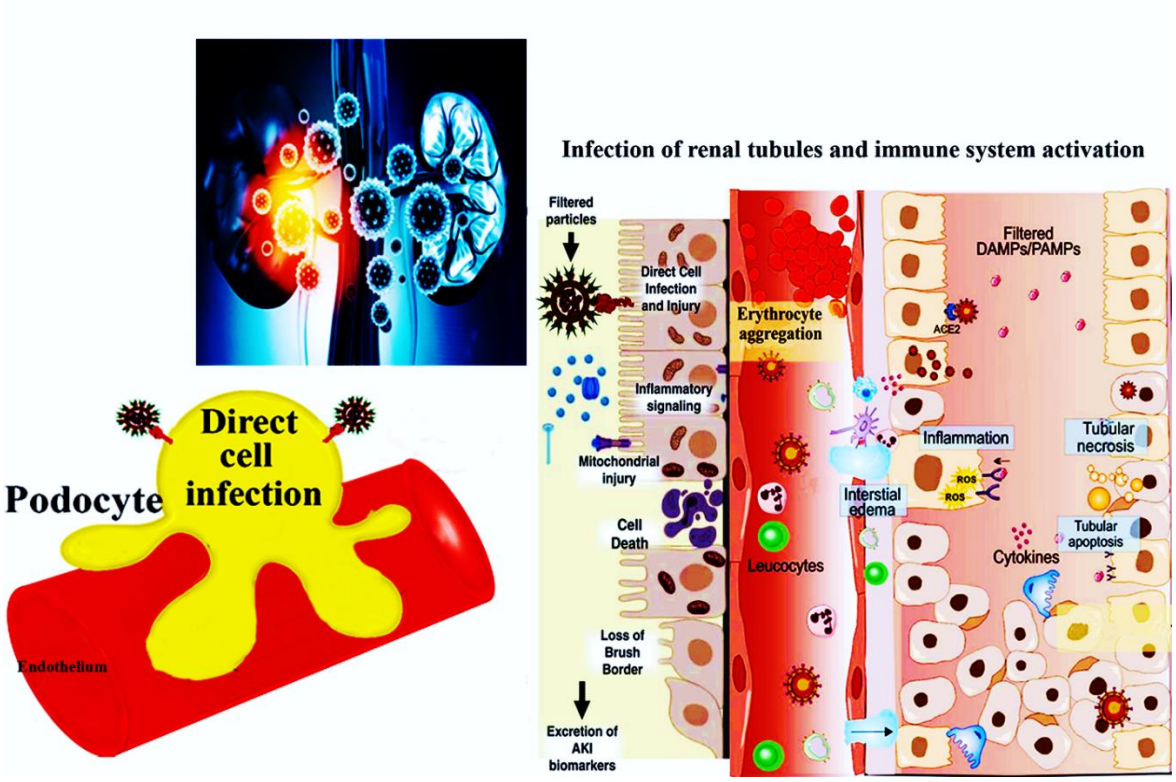

Figure 1. Possible Pathophysiological Mechanisms of Kidney Injury by SARS-CoV-2.[46-48]

4. Organ crosstalk

Lung-kidney crosstalk: the kidney-lung crosstalk can lead to cytokine storm, multi-organ failure and death.[40] The most important reasons for the occurrence of kidney-lung crosstalk are: At first, SARS-CoV-2 binds the receptor ACE2 on host cells. Actually, ACE2 expression in kidney cells was not less than that in the lung. Secondly, the kidney and lung have reciprocal effects on each other. It can be mentioned that kidney impairment and death of renal tubular epithelial cells cause severe damage of the lung and accelerate the inflammation progress in the lungs. Lung dysfunctions could damage the kidney through inflammatory reactions.[37,40] Acute Respiratory Distress Syndrome (ARDS) can also cause renal medullary hypoxia.[42] In addition, heart–kidney crosstalk: cardiomyopathy and

acute viral myocarditis lead to renal vein congestion, hypotension, and renal hypo-perfusion and finally heart–kidney crosstalk causes reduction of glomerular filtration rate and AKI.[42]

5. State of dehydration, leading to pre-renal failure with acute tubular necrosis

Fever and reduced consumption of fluids in patients can cause dehydration. The different consequences of dehydration on kidney function include decreasing of glomerular filtration rate and AKI.[32,38]

6. Nephrotoxicity caused by the drug

Injury to the liver and kidneys can impair metabolism, excretion, dosing and expected concentrations of the drugs prescribed for the treatment of COVID-19 including Oseltamivir, Ribavirin, Lopinavir/Ritonavir, Chloroquine Phosphate and Hydroxy Chloroquine Sulfate, which can increase the risk of their toxicity.[45]

The synergistic effect of all these factors and mechanisms has been associated with an increased incidence of AKI and death in severe cases of COVID-19.[40,42]

Conclusion

COVID-19 is the worst pandemic disease of modern times caused by SARS-CoV-2. Kidney impairment and abnormality of renal function are major complications of COVID-19. This study reviewed the precise impact of COVID-19 on the structure and functions of the kidney. Based on the results of the present study, it can be concluded that podocytes and proximal straight tubular cells are potential host cells targeted by SARS-CoV-2. The outcomes of novel virus infection are diverse, ranging from proteinuria to acute kidney injury. The pathophysiological mechanisms of kidney involvement in COVID-19 patients are: direct infection of tubules, dehydration, cytokine storm and maladaptive systemic inflammatory immune response, organ crosstalk and drug-induced cytotoxicity. Therefore, we need to pay more attention to the regularly monitoring of renal function and treatment strategy against the infection of SARS-CoV-2 to the renal tissue.

Conflict of Interest

The authors declare that they have no conflicts interest.

References

1. Wang L, Li X, Chen H, Yan S, Li Y, Li D, ET AL. SARS-CoV-2 infection does not significantly cause acute renal injury: an analysis of 116 hospitalized patients with COVID-19 in a single hospital, Wuhan, China. medRxiv. 2020. doi:10.1101/2020.02.19.20025288
2. Perico L, Benigni A, Remuzzi G. Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade. Nephron. 2020;144(5):213-21. doi:10.1159/000507305
3. Ramphul K, Mejias SG. Coronavirus disease: a review of a new threat to public health. Cureus. 2020;12(3):e7276. doi:10.7759/cureus.7276
4. Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. Eur Radiol. 2020;30(6):3306-9. doi:10.1007/s00330-020-06731-x
5. Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-converting enzyme 2 and antihypertensives (angiotensin receptor blockers and angiotensin-converting enzyme inhibitors) in coronavirus disease 2019. Mayo Clin Proc. 2020;95(6):1222-30. doi:10.1016/j.mayocp.2020.03.026
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. doi:10.1001/jama.2020.1585
7. Tolouian R, Vahed SZ, Ghiyasvand S, Tolouian A, Ardalan M. COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment. J Renal Inj Prev. 2020;9(2):e19. doi:10.34172/jrip.2020.19
8. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020;382(17):1653-9. doi:10.1056/NEJMsr2005760
9. Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol. 2005;79(23):14614-21. doi:10.1128/JVI.79.23.14614-14621.2005
10. Ye M, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. J Am Soc Nephrol. 2006;17(11):3067-75. doi:10.1681/ASN.2006050423
11. Ferrario CM, Varagic J. The ANG-(1–7)/ACE2/mas axis in the regulation of nephron function. Am J Physiol Renal Physiol. 2010;298(6):F1297-305. doi:10.1152/ajprenal.00110.2010
12. Wang Z, Xu X. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, Leydig and Sertoli cells. Cells. 2020;9(4):920. doi:10.3390/cells9040920
13. Yao H, Lu X, Chen Q, Xu K, Chen Y, Cheng L, et al. Patient-derived mutations impact pathogenicity of SARS-CoV-2. MedRxiv. 2020. doi:10.1101/2020.04.14.20060160
14. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185-92. doi:10.1007/s11684-020-0754-0
15. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney impairment is associated with in-hospital death of COVID-19 patients. MedRxiv. 2020. doi:10.1016/j.kint.2020.03.005
16. Xiao G, Hu H, Wu F, Sha T, Zeng Z, Huang Q, et al. Acute kidney injury in patients hospitalized with COVID-19 in Wuhan, China: a single-center retrospective observational study. Nan fang yi ke da xue xue bao. 2021;41(2):157-63. doi:10.12122/j.issn.1673-4254.2021.02.01
17. Mubarak M, Tolouian R, Pezeshgi A. Collapsing glomerulopathy following COVID-19 infection; possible relationship with APOL1 kidney risk alleles in African-Americans. Immunopathol Persa. 2020;6(2). doi:10.34172/ipp.2020.18
18. Zhang YM, Zhang H. Genetic roadmap for kidney involvement of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Clin J Am Soc Nephrol. 2020;15(7):1044-6. doi:10.2215/CJN.04370420
19. Trimarchi H. SARS-CoV-2 and Fabry nephropathy: potential risks and the pathophysiological perspective. J Nephropathol. 2020;9(4):e36. doi:10.34172/jnp.2020.36
20. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2

and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80. doi:10.1016/j.cell.2020.02.052
21. Meng T, Cao H, Zhang H, Kang Z, Xu D, Gong H, et al. The insert sequence in SARS-CoV-2 enhances spike protein cleavage by TMPRSS. biorxiv. 2020. doi:10.1101/2020.02.08.926006
22. Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. 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
23. South AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin–angiotensin system inhibition during the COVID-19 pandemic. Nat Rev Nephrol. 2020;16(6):305-7. doi:10.1038/s41581-020-0279-4
24. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46(4):586-90. doi:10.1007/s00134-020-05985-9
25. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417-8. doi:10.1016/S0140-6736(20)30937-5
26. Kissling S, Rotman S, Gerber C, Halfon M, Lamoth F, Comte D, et al. Collapsing glomerulopathy in a COVID-19 patient. Kidney Int. 2020;98(1):228-31. doi:10.1016/j.kint.2020.04.006
27. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. J Am Soc Nephrol. 2020;31(8):1683-7. doi:10.1681/ASN.2020040432
28. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219-27. doi:10.1016/j.kint.2020.04.003
29. Wang K, Chen W, Zhou YS, Lian JQ, Zhang Z, Du P, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. biorxiv. 2020. doi:10.1101/2020.03.14.988345
30. Kosugi T, Maeda K, Sato W, Maruyama S, Kadomatsu K. CD147 (EMMPRIN/Basigin) in kidney diseases: from an inflammation and immune system viewpoint. Nephrol Dial Transplant. 2015;30(7):1097-103. doi:10.1093/ndt/gfu302
31. Diao B, Wang C, Wang R, Feng Z, Zhang J, Yang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. Nat Commun. 2021;12(1):2506. doi:10.1038/s41467-021-22781-1
32. Fortarezza F, Pezzuto F. COVID-19 nephropathy: what could pathologist say?. J Nephropathol. 2020;9(4):e32. doi:10.34172/jnp.2020.32
33. Micarelli D, Moccia F, Costantini S, Feriozzi S. COVID-19 is a complex disease with wide spectrum of clinical patterns and an emerging problem for nephrologist. J Nephropathol. 2020;9(4):e33. doi:10.34172/jnp.2020.33
34. Mubarak M, Nasri H. COVID-19 nephropathy; an emerging condition caused by novel coronavirus infection. J Nephropathol. 2020;9(3):e21. doi:10.34172/jnp.2020.21
35. Khouchlaa A, Bouyahya A. COVID-19 nephropathy; probable mechanisms of kidney failure. J Nephropathol. 2020;9(4):e35. doi:10.34172/jnp.2020.35
36. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The novel coronavirus 2019 epidemic and kidneys. Kidney Int. 2020;97(5):824-8. doi:10.1016/j.kint.2020.03.001
37. Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on kidney dysfunctions of COVID-19 patients. MedRxiv. 2020. doi:10.1101/2020.02.08.20021212
38. Valizadeh R, Baradaran A, Mirzazadeh A, Bhaskar LV. Coronavirus-nephropathy; renal involvement in COVID-19. J Renal Inj Prev. 2020;9(2):e18. doi:10.34172/jrip.2020.18
39. Durvasula R, Wellington T, McNamara E, Watnick S. COVID-19 and kidney failure in the acute care setting: our experience from Seattle. Am J Kidney Dis. 2020;76(1):4-6. doi:10.1053/j.ajkd.2020.04.001
40. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102-8. doi:10.1016/j.jpha.2020.03.001
41. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol. 2020;92(6):595-601. doi:10.1002/jmv.25726
42. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol. 2020;16(6):308-10. doi:10.1038/s41581-020-0284-7
43. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
44. Jin GY, Jin LL, Zheng J, He BJ. Advantages of anti-inflammatory acupuncture in treating sepsis of coronavirus disease 2019. World J Tradit Chin Med. 2020;6(2):188. doi:10.4103/wjtcm.wjtcm_12_20
45. Rismanbaf A, Zarei S. Liver and kidney injuries in COVID-19 and their effects on drug therapy; a letter to editor. Arch Acad Emerg Med. 2020;8(1):e17.
46. Bierzynska A, Soderquest K, Koziell A. Genes and podocytes–new insights into mechanisms of podocytopathy. Front Endocrinol. 2015;5:226. doi:10.3389/fendo.2014.00226
47. 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. doi:10.1002/rmv.2176
48. Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2?. Am J Physiol Renal Physiol. 2020;318(6):F1454-62. doi:10.1152/ajprenal.00160.2020