Title: The lethal internal face of the coronaviruses: Kidney tropism of the SARS, MERS, and COVID-19 viruses

Authors and Affiliations: Roza Motavalli [1], Walid Kamal Abdelbasset [2, 3], Heshu Sulaiman Rahman [4], Muhammad Harun Achmad [5], Angelina Olegovna Zekiy [6], Ali Adili [7], Farhad Motavalli Khiavi [8], Faroogh Marofi [9, 10], Mehdi Yousefi [11], Shadi Ghoreishizadeh [10], Navid Shomali [10, 11], Jalal Etemadi [12*], Mostafa Jarahian [13*]

1. Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
2. Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia
3. Department of Physical Therapy, Kasr Al-Aini Hospital, Cairo University, Giza, Egypt
4. Department of Physiology, College of Medicine, University of Sulaimani, Suleimanyah, Iraq
5. Department of Pediatric Dentistry, Faculty of Dentistry, Hasanuddin University, Indonesia (Lecture of Pediatric Dentistry)
6. Sechenov First Moscow State Medical University, Moscow, Russian Federation
7. Department of oncology, Tabriz University of Medical Sciences, Tabriz, Iran
8. Department of Virology, Pasteur Institute of Iran, Tehran, Iran
9. Department of Immunology, Division of Hematology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
10. Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
11. Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
12. *Toxicology and Chemotherapy Unit (G401), German Cancer Research Center (DKFZ), Heidelberg, Germany
13. *Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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*Corresponding author: Jalal Etemadi, Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. Email: jalaletemadi@yahoo.com

And

*Corresponding author: Mostafa Jarahian, Toxicology and Chemotherapy Unit (G401), German Cancer Research Center, 69120, Heidelberg, Germany. Email: jarahianmostafa@gmail.com

Abstract

The kidney is one of the main targets attacked by viruses in patients with a coronavirus infection. Until now, SARS-CoV-2 has been identified as the seventh member of the coronavirus family capable of infecting humans. In the past two decades, humankind has experienced outbreaks triggered by two other extremely infective members of the coronavirus family; the MERS-CoV and the SARS-CoV. According to several investigations, SARS-CoV causes proteinuria and renal impairment or failure. The SARS-CoV was identified in the distal convoluted tubules of the kidney of infected patients. Also, renal dysfunction was observed in numerous cases of MERS-CoV infection. And recently, during the 2019-nCoV pandemic, it was found that the novel coronavirus not only induces acute respiratory distress syndrome (ARDS) but also can induce damages in various organs including the liver, heart, and kidney. The kidney tissue and its cells are targeted massively by the coronaviruses due to the abundant presence of ACE2 and Dpp4 receptors on kidney cells. These receptors are characterized as the main route of coronavirus entry to the victim cells. Renal failure due to massive viral invasion can lead to undesirable complications and enhanced mortality rate, thus more attention should be paid to the pathology of coronaviruses in the kidney. Here, we have provided the most recent knowledge on the coronaviruses (SARS, MERS, and COVID19) pathology and the mechanisms of their impact on the kidney tissue and functions.

Key Words: SARS, MERS, COVID19, Kidney, Viral Infection

Abbreviations

CoVs: Coronaviruses; **MERS-CoV**: Middle East respiratory syndrome coronavirus; **SARS-CoV**: Severe acute respiratory syndrome coronavirus; **COVID19**: Coronavirus disease 2019; **AKI**: Acute kidney injury; **ARV**: Antiretroviral; **ACE**: Angiotensin-converting enzyme; **DPP4**: Dipeptidyl peptidase 4 ; **DCs**: Dendritic cells; **FGF2**: Fibroblast growth factor 2; **NK cells**: Natural killer cells; **ROS**: Reactive oxygen species; **HIF-1**: Hypoxia-inducible factor 1; **CK**: Creatine kinase; **IL**: Interleukine; **BUN**: Blood urea nitrogen; **qRT-PCR**: Real-Time quantitative reverse transcription PCR; **eGFR**: Estimated Glomerular Filtration Rate; **sCr**: Serum creatinine; **CKD**: Chronic kidney disease; **ADAM17**: A disintegrin and metalloprotease 17; **AT1**: Angiotensin II type 1; **Ang II:** Angiotensin II; **JAK/ STAT**: The Janus kinase/Signal transducer and activator of transcription; **PI3K/ AKT**: The phosphatidylinositol 3 kinase/Protein kinase B; **MAPK/ ERK**: Mitogen-activated protein kinase/Extracellular signal-related kinases; **ATN**: Acute tubular necrosis; **NSAIDs**: Non-steroidal anti-inflammatory drugs; **hrsACE2**: Human recombinant soluble ACE2.

1. Introduction

Kidney involvement is the main complication in patients infected with diverse types of coronavirus. Principally, this is owing to the infection of renal cells by the virus itself; antiretroviral (ARV) medications and attendance of other risk factors such as hypertension, diabetes mellitus, hepatitis C virus; and illegal medication usage (1). Human coronaviruses enveloped RNA viruses with a single-stranded RNA genome of positive polarity, are not novel, and were first recognized in the mid-1960s and typically lead to slight to modest upper-respiratory tract sicknesses (2). Coronaviruses (CoVs) are memberships of the Corona virinae subfamily of the Corona viridae family. Corona virinae subfamily includes 4 virus clusters: α coronavirus, β coronavirus, and γ coronavirus and the last cluster is a conditionally allocated novel cluster named delta coronaviruses. Overall, all identified human coronaviruses belong to the types of α coronavirus (HCoV-NL63 and HCoV-229E) and β coronavirus (HCoV-HKU1, HCoV-OC43, and SARS-CoV) (3). Major human infections with zoonotic coronaviruses including the Middle East Respiratory Syndrome Coronavirus (MERS)-CoV Severe Acute Respiratory Syndrome (SARS)-CoV, and a new coronavirus (2019-nCoV) COVID19, have raised great public health concern globally. In all eras, viral infections are the most prevalent infectious illnesses and are frequent stimulators for establishing major socio-economic, clinical, and biological issues worldwide. Nearly, all types of coronaviruses are dispersed broadly among animals and humans and trigger neurologic, hepatic, enteric, and respiratory diseases. Up to now, COVID19 is the seventh participant of the coronaviruses family that contaminates humans. A few years earlier the 2019-nCoV epidemic, the current century has previously seen outbreaks triggered by two other extremely infective coronaviruses, the MERS-CoV and the SARS-CoV. An

investigation disclosed that SARS-CoV infection displayed 84.6% of proteinuria on dipstick tests and 6.7% of acute kidney injury (AKI) and also identified SARS-CoV in the distal convoluted tubules of the kidney (13). In line with this consideration, kidney involvement in human coronavirus patients was detected in the SARS-CoV epidemic in the initial 2000 (4). Furthermore, numerous cases of MERS-CoV infection have been shown to impair kidney function (5, 6), and some of the involved cases need renal replacement therapy. Accumulating data of clinical practice have discovered that infection with COVID19 not only induces severe acute respiratory syndrome but also several organ damages, including hepatic, myocardial, and acute kidney injury (7). Furthermore, the kidney plays a momentous character in the metabolism and elimination of several antiretroviral drugs and this triggers the kidney to be more vulnerable to numerous kinds of damages, including nephrolithiasis, obstructive nephropathy, acute kidney injury, interstitial nephritis, and tubular dysfunction, thus it should be paid more consideration to the involvement of kidney in coronavirus infections. Our aim in this study is to compare kidney involvement in three types (SARS, MERS, and COVID19) of coronavirus outbreaks.

2. Pathogenesis of kidney injury

Up to now, the precise mechanism of kidney involvement is indistinct: assumed mechanisms include straight cellular lesions due to the virus or sepsis leading to cytokine storm syndrome. It has been revealed that dipeptidyl peptidase-4 and ACE, both expressed on renal tubular cells, were recognized as binding spouses for MERS-CoV and SARS-CoV, respectively (8, 9). The most significant discovery was the surface expression of ACE2 protein on enterocytes of the small intestine and lung alveolar epithelial cells. Additionally, ACE2 existed in arterial smooth muscle cells and venous and arterial endothelial cells in all studied organs (10). It has been also revealed that in the kidney ACE2 spreads to the luminal surface of tubular epithelial cells (11). Studies have revealed that coronavirus enters into the target cells through ACE2 receptors, which are broadly accessible in the renal cells (12-14). Furthermore, ACE expression is entirely abundant in the human renal cells at least 5 times more than what has been discerned in the respiratory tract (15). Functionally, two forms of ACE2 is existing. The full-length ACE2 comprises a structural transmembrane domain, which anchors its extracellular domain to the plasma membrane. The extracellular domain has been revealed as a receptor for the spike (S) protein of SARS-CoV (16), and recently, for the COVID19 (17, 18). The soluble form of ACE2 lacks the membrane anchor and circulates in small amounts in the blood (19). We propose that this soluble form may act as a competitive interceptor of

SARS-CoV and other coronaviruses by preventing the binding of the viral particle to the surface-bound, full-length ACE2. Indeed, *in-vitro* studies showed that SARS-CoV replication was blocked by a soluble form of ACE2 in the monkey kidney cell line, Vero-E6 (20, 21). Moreover, ACE2 fused to the Fc portion of immunoglobulin has just been reported to neutralize COVID19 *in-vitro* (22) and the COVID19 binds ACE2 with a higher affinity than SARS-CoV (23). The pathogenicity mechanism of the MERS disease has been clarified in recent investigations. The spike glycoprotein (S) of MERS-CoV adherence to the cellular receptor, dipeptidyl peptidase 4 (DPP4) (24, 25). DPP4 is extensively expressed on epithelial cells in the liver, small intestine, prostate, alveoli, kidney, and on some activated leukocytes (26), offering that the span of MERS-CoV tissue tropism is wider than that of any other coronavirus (27). Hence, MERS-CoV can contaminate numerous human immune cells, including T-cells (28), macrophages, and dendritic cells (DCs) (29). Stimulation of DCs and macrophages after MERS-CoV infections, lead to the vigorous and constant production of pro-inflammatory chemokines and cytokines (29, 30). Additionally, it has been revealed that MERS-CoV can also stimulate apoptosis of both lung and kidney cells via upregulation of fibroblast growth factor 2 (FGF2) and Smad7 expression (31).

3. Indirect effects of viral infection

Taken together, cytokines release might apply indirect effects on renal tissue, including rhabdomyolysis, shock, and hypoxia (32). Moreover, the augmented occurrence of AKI in COVID19 affected persons could be owing to the synergistic effect of all of these factors and also by drug-induced nephrotoxicity, toxic tubular impairment, and even a state of dehydration (33, 34). Also, cytokine storm syndrome is suggested as a causative mechanism in COVID19 induce AKI. Besides, other potential mechanisms of renal impairment including the occurrence of uncontrolled diabetes or hypertension and improper utilization of non-steroidal anti-inflammatory drugs (NSAIDS) (35, 36). Finally, the potential relationship between AKI and coagulation disorder in COVID19 patients remains to be determined (Table 1).

4. Direct viral effects

COVID19 might lead to tubular injury via infiltrating renal parenchyma by pro-inflammatory cells. Furthermore, it has been discovered that inflammatory cells like CD56+ natural killer cells, CD4+ T cells, and CD68+ macrophages, can be existing in the renal interstitium (37). Subsequently, the unlimited activation of these immune cells may finally

promote epithelial cell apoptosis, induce microvasculature alteration, and stimulate fibrosis (38). Additionally, expression of C5b-9, identified also as membrane attack complex is lacking in normal kidneys. Nonetheless, the formation of C5b-9 complexes has been revealed to stimulate renal parenchymal cells to produce reactive oxygen species (ROS), release pro-inflammatory cytokines, and kidney damaging pro-fibrotic factors (39). Since the kidney is the most susceptible organ to hypoxia, inadequate blood flow may cause AKI (ischemic ATN) and ischemia can motivate HIF-1 (hypoxia-inducible factor 1) and then ROS creation of mitochondrial dysfunction (36, 40). Cumulative evidence demonstrated that HIF-1 triggers genes that stimulate the synthesis of fibrous connective tissue which impedes the kidney's ordinary function and improves effector T cell function, including elevation of cytolytic activity and producing inflammatory cytokine while ROS annihilates the molecular ingredients of nephron prompting a cells injury and/or death (32, 40, 41). It is noteworthy, direct virus invasion to the interstitium and renal tubular or glomerular cells is probable, ever since the straight cytopathic effect of the virus on numerous kidney cells has been distinguished in former investigations (4, 42, 43). A large amount of data from previous studies display that, the glomerulopathy resulting from coronaviruses was reported to be low, while immune complexes deposition of viral elements or virus-induced specific immunological abnormalities is possible (Table 1) (32, 34, 44).

5. Kidney impairment in Severe Acute Respiratory Syndrome (SARS)

SARS-COV infection is a quickly mortal pulmonary infection that initially occurred in China in late 2002 (45). The pathogenesis of SARS is extremely intricate, with several elements leading to violent damage in the lungs and the distribution of the virus to some other tissues such as renal cells (46). Although the exact distribution mechanism remains unclear, it has been hypothesized that a patient with renal failure might transmit an extremely high viral load. Furthermore, it would be exciting to understand whether the clinical sequence of a SARS patient with renal impairment would be diverse from that of other SARS cases. Notably, a substantial number of cases with acute renal dysfunction can be discovered among patients with confirmed SARS-CoV. A rudimentary investigation of 12 SARS-affected patients who established AKI reports a great mortality rate of 77% (47, 48). Furthermore, among 536 SARS patients in this retrospective study, 6.7% of this group had elevated plasma creatinine concentration through the later period of the infection regardless of the normal level at primary presentation. Also, patients who afterward advanced renal deterioration had clinical exhibitions parallel to the symptomatology of SARS patients in former findings (49).

It has been revealed that SARS patients with rhabdomyolysis have a high occurrence of AKI, bacterial infection, and death (50, 51). Despite this consideration, it has been discovered that impaired renal function with elevated plasma creatinine is not a prevalent finding in a large number of SARS patients at the time of initial clinical presentation but conveys unexpected mortality (4). The advancement of AKI is a significant negative prognostic index for durability with SARS. The direct or indirect reasons for AKI in affiliation with SARS are unclear and hypothesize that elevate in creatine kinase (CK) may perform a significant rule. Correspondingly, it has been proven that cytokines such as IL-8 and IL-6 induced by viral infections have been involved as playing a fundamental role in renal failure. These elevated cytokines in SARS were associated with a reduced number of lymphocyte counts. The elevated cytokines, in collaboration with lymphokines, cause the adherence of inflammatory cells to endothelium and other damaged locations (52, 53). Taken together, these discoveries recommend that in SARS disease, kidney impairment, as well as lung damage, is associated with immune injury as a consequence of unconventional host response, rather than uninhibited viral replication.

It has been shown that hypouricemia is prevalent in SARS patients. Generally, hypouricemia triggered by uricosuria has been revealed in cases with chronic and acute tubule interstitial nephritis, but seldom has been testified in people with systemic infections without the obvious renal disorder (54, 55). Albeit the mechanism is not clarified, renal hypouricemia in patients with systemic infections has been revealed to be a factor in poor prognosis (56). The result of studies revealed that more than 25 percent of patients suffering from SARS had hypouricemia, a clinical specification not reported formerly (57, 58). The reverse association between serum uric acid level and fractional excretion of uric acid displays that the hypouricemia in SARS patients caused by a surge in uric acid excretion throughout SARS-CoV infection. In summary, hypouricemia resulting from abnormal renal urate handling is not uncommon in patients with SARS-CoV infection and may reflect the severity of the disease and predict poor patient outcomes. Surprisingly 17 years after the SARS-COV outbreak, a similar picture was created by COVID 19. Werion A *et al.* reported that hypouricemia was independently associated with an increased risk of respiratory failure in a cohort of COVID 19 patients who required hospitalization (Table 1) (59).

6. Renal involvement in Middle East Respiratory Syndrome (MERS)

In September 2012 for the first time, MERS-CoV was recognized in Saudi Arabian people with respiratory failure. Since the early case of MERS-CoV, there have been 688 confirmed cases and 282 deaths in 20 countries and indeed the mortality rate of MERS (~43%) is much higher than that for SARS (~10%) (60). The clinical manifestation of MERS-CoV infection is specified by severe pneumonia and respiratory failure, similar to SARS-CoV (61). On the other hand, indicators of renal function, such as creatinine levels and blood urea nitrogen (BUN), are commonly not accessible in some of the issued cohorts, but according to the latest WHO summary declaration, some acute patients established renal failure during their clinical course (62, 63). Surprisingly, increasing pieces of evidence show that AKI was characterized in some MERS patients, with a possible effect on disease severity (31, 64, 65). Chan *et al.* claimed that AKI is one of the main clinical presentations and seen in at least six of the 34 reported cases. Most of the residual 28 patients maybe also experienced renal function deterioration, although their study details were not accessible. This finding was uncommon, even when compared to SARS in which 28.8% of the cases had an abnormal urinalysis and noticeable viral load by qRT-PCR in urine, while just 6.7% advanced ARF with a histological indication of acute tubular necrosis, and most of them did not necessitate renal replacement therapy (62). Entirely, this clinical demonstration associates with the *in vitro* evidence of competent replication of MERS-associated CoV in kidney cell lines, including LLC-MK2, Vero, HEK 293, and 769P (66, 67). More notably, the incidence of renal contribution seemed to be a meager prognostic factor, as those with renal failure either died or needed renal replacement therapy, while two patients without renal impairment persisted. It has been recommended that alterations in kidney cell contribution might happen during MERS- and SARS -CoV infection (68, 69). Regarding the SARS patients, AKI happens somewhat late in the development of sickness after a median of three weeks from the advent of the first presentation (70, 71). However, Eckerle *et al.* showed that ARF happened much sooner, explicitly in 6 of 9 infectious cases after a median of 11 days (68). Intriguingly, the absence of further pulmonary injuries detected in the macaque model of MERS-CoV infection proposed that AKI was more probable owing to hypoxic impairment than a straight viral cytopathic effect (72). The precise intrusion of MERS-CoV with the induction of the interferon response offers one of the numerous probable elucidations for an augmented capacity of MERS-CoV to duplicate in kidney cells (73). Eventually, we can appraise that the renal pathological changes related to human coronavirus may be triggered indirectly by a harmful immune response or cytokine reaction induced by a viral infection and a systemic

toxic response subsequent from respiratory defeat or as well as directly by the cytopathic effect mediated by virus replication (8).

7. Kidney injury in COVID19

Analysis of genetic sequence discovered that the COVID19 belongs to the β-coronavirus genus, with an about 80% nucleotide personality to SARS-CoV and an approximately 52% similarity to MERS-CoV (74). The principal presentation of COVID19 is a severe respiratory disease with alveolar and interstitial pneumonia, but it can affect numerous organs such as the blood, digestive tract, heart, kidney, and nervous system (75). The fast distribution outbreak, which primarily appeared in Wuhan, Hubei Province, China, in December 2019, has since been expressed as a worldwide pandemic. In preceding reports of MERS-CoV and SARS infections, AKI established in 5% to 15% patients and carried a high (60%–90%) mortality rate, while initial reports proposed a lesser occurrence (3%–9%) of AKI in those with COVID-19 infection carrying mortality of about 3.7% (75-77). Increasing evidence demonstrated that 2019-nCoV can trigger AKI in COVID-19 patients (78, 79). It has been revealed that AKI is one of the significant complications of the COVID19, happening in 0.5–7% of patients and 2.9–23% of ICU hospitalized persons (80, 81). On the other hand, whether the AKI of 2019-nCoV is triggered by a cytokine storm-induced systemic inflammatory response or coronavirus-induced cytopathic effect remains obscure. In line with these statements, Pan *et al.* stated that the cytopathic effects of COVID19 on proximal tubule cells and podocytes may trigger AKI in cases with COVID19, particularly in persons with COVID19 infection in blood samples. So, investigators need to be more considerate of the initial monitoring of kidney function and carefully deal with the urine of COVID19 cases with AKI to inhibit unintentional infection (82). Notably, most COVID19 patients established AKI in the initial stage of hospitalization, particularly in just 48 hours after admission in patients with elevated baseline sCr. In the treatment of COVID19, initial inhibition of kidney deterioration, consist of avoiding nephrotoxic medications and sufficient hemodynamic support, is principally vital and initial renal replacement therapy may advance the patients' prognosis (83). On the other hand, beyond inadequacy in kidney task, the atypical urine findings, consist of hematuria and proteinuria, were also related to in-hospital death. This illustrated that more consideration should be paid to a urine test. Taken together, these outcomes recommend a relationship between AKI at the primary phase and the severity of COVID19 patients. As mentioned in the previous discussion, AKI consequences from a sudden loss of kidney task and are certainly related to enhanced morbidity and mortality (84).

Overall, we realized that patients with increased sCr were more probable to progress AKI throughout hospitalization, which is in keeping with the investigation in SARS, so it is essential to enhance the awareness of AKI in cases who entered the hospital with increased sCr (85). According to one cohort, the AKI detection rate in patients with COVID19 was 5.1%, which is consistent with the latest reports of little sample size (76, 86, 87) and much higher than the 0.5% of a large observational study (88). One potential clarification of the high incidence of renal involvement at hospital admission is that most of the people with COVID19 had a previous history of mild renal impairment. In line with this consideration, Cheng *et al.* claimed that there is a strong association between kidney involvement and poor consequence in people with COVID19. They observed a high incidence of kidney involvement in COVID-19 hospitalized patients and more than 40% of patients indicated renal failure, with enhanced BUN and sCr values in over 13% of them. The finding of the mentioned study also displayed a poor prognosis irrespective of early COVID19 severity and general physical condition (89). Furthermore, Li *et al.* analyzed renal function in 59 COVID19 infected persons including 28 identified as acute cases and 3 deaths. According to this study, proteinuria was detected in 63% of patients. Additionally, elevated amounts of BUN and sCr were diagnosed in 27% and 19% of their patients, respectively (90). Moreover, a CT scan of the kidneys from 27 infected persons displayed edema and inflammation of the renal parenchyma in whole patients (100%) (34). Similarly, a consecutive analysis of 710 COVID19 patients admitted to a hospital in Wuhan (2020), exhibited the presence of hematuria in 26.9% and proteinuria in 44% of infected persons(91). Likewise, elevated BUN and sCr were respectively observed in 14.1% and 15.5% of their patients. AKI was also detected in 3.2% of infected cases. Afterward, survival curves imagined through Kaplan-Meier analysis revealed that the renal impairment had a tremendous hazard for in-hospital mortality. According to the Cox regression model, elevated BUN and plasma creatinine, hematuria, proteinuria, and AKI were independent risk factors for forecasting in-hospital patients mortality(32).

In a study, Xu *et al.* revealed that 15.8% of COVID19 patients were complicated by AKI on admission. Noticeably, the levels of uric acid, BUN, and sCr on admission were upper in acute ill persons than those of mild patients. Furthermore, these outcomes displayed that old age and diabetes were the main risk factors of AKI at the primary phase of COVID19 patients. Among 56 patients suffering from AKI at the initial stage of admission, roughly a third of subjects died in the first ten days after hospitalization (92). Remarkably, it has been

shown that the fatality rate is greater among COVID19 persons with AKI compared to those without AKI (92). Accordingly, these findings provide evidence that AKI at the initial phase enhanced the mortality risk of COVID19 infected patients. In a study performed by Naicker *et al.* among 59 patients with COVID-19 on day 1 of illness, 34% of patients have had albuminuria, and 63% of patients have had proteinuria during their stay in hospital (93). Diao *et al.* found that 27.06% of subjects with COVID19 had abnormal eGFR, proposing that acute renal injury is comparatively prevalent following COVID19 infection (37). Interestingly, this phenomenon is diverse from the SARS outbreak in 2003, in which AKI was rare although it was one of the highest risk factors of mortality (70). Diao *et al.* strongly recommend that renal tubular injury is straightly triggered by viral infection and replication because of COVID19 (37). Eventually**,** this phenomenon is in keeping with its other resemblances to MERS-CoV and SARS-CoV, both of which can also infect human kidneys (94, 95). Lately, Zhao *et al.* reported virus fragments obtained from the urine of COVID19 infected patients and revealed that the kidney is the place for viral infection and replication outside of the respiratory system, suggesting the viral fragments originated from the kidney may enter the urine via glomerular filtration (96). A meta-analysis conducted by Henry *et al.* revealed that CKD was correlated with an elevated risk of severe 2019-nCoV infection (97). Hence, individuals suffering from CKD should be recommended to take additional precautions to diminish exposure to the virus. Thus, CKD shall be considered as a significant factor in upcoming risk stratification models for COVID19. In another investigation, Diao and colleagues (37, 98) analyzed the viral nucleocapsid protein in situ in the kidney post-mortem and realized that COVID19 antigens gathered in kidney tubules, proposing that COVID19 directly infects the human kidney. Significantly, the alteration between the greater renal tropism of COVID19 against SARS-CoV could be clarified by the enhanced affinity of 2019-nCoV for ACE2, allowing higher infection of the renal tissue, which might perform as a viral reservoir (99).

Cell infection through SARS viruses which bind to ACE2 leads to suppression of ACE2 activity following increased ACE2 shedding via over activation of ADAM17 (100) and decrease of ACE2 expression via membrane fusion and virus entry into infected cells. As a result, the *Angiotensin II/Mas receptor* pathway is noticeably downregulated via augmentation of the Angiotensin II type 1 (AT1) receptors pathway (101, 102). It was assumed ACE1/ ACE2 imbalance and augmented Ang II/ AT1 signaling besides attenuate Ang (1–7)/Mas signaling pathway that arise from SARS-CoV-2 infection, presents a

prominent role in tissue damages. The results reveal that augmentation in the Ang II/AT1R axis trigger servals pathways including PI3K/Akt, JAK/STAT, ERK/MAPK (103)which leads to overexpression of inflammatory factors, HIF-1, ROS, fibrosis factors (104). Following overexpression mention factors fibrosis, apoptosis, cytokine storm, infiltration of immune cells have happened in this line. Altogether these complications along with direct viral invasion and rhabdomyolysis terminate to appropriate indications of kidney disfunction comprising ATN, interstitial inflammation, podocytes injury, microangiopathy, hypercoagulation (Figure1) (105).

Additionally, persons infected with COVID19 appear to be affected by AKI more commonly than patients with SARS-CoV(34). On the other hand, referring to the information from 2 recent studies (106, 107) AKI was infrequent in 2019-nCoV, and COVID19 infection does not result in apparent azotemia and AKI. While some other discoveries illustrate that AKI could be one of the risk factors for mortality in COVID19 patients. Finally, according to the data from current investigations, the main findings include: (1) AKI is more prevalent in seriously ill patients with COVID19; (2) Male elderly 2019-nCoV patients with diabetes mellitus are more vulnerable to AKI; (3) AKI at the initial phase promotes demise risk of COVID19 infected subjects(92). Monitoring kidney function must therefore be highlighted even in subjects with slight respiratory involvement, and changed kidney function should be given specific consideration after hospitalization in clinical practice. As a final point, in the lack of specific treatment, prompt recognition, applying supportive care, sufficient hemodynamic support, appropriate use of continuous renal replacement therapy, and cytokine removal strategies, may help to improve the prognosis of COVID19 patients with AKI (108).

8. AKI management strategy in COVID-19 patients

Global guidelines for the management of Covid-19-induced AKI recommend several methods in which the leading therapeutic approaches fall into two categories. First, disease management based on standard criteria (hemodynamic optimization, renal function and AKI stage, management of nephrotoxin and fluids); Second, management based on experimental strategies (non-steroidal anti-inflammatory drugs (NSAIDs), systemic coagulation, immunomodulatory agents, antivirals, ACE inhibitors, human recombinant soluble ACE2 (hrsACE2), Serine protease inhibitors (serpins) (109-111).

9. Conclusion

Taken together, findings from previous investigations, propose that the occurrence of AKI was not unusual in MERS and SARS and carries a high mortality. Notably, they happen in patients complicated with ARDS or several organ impairments, and the progress of AKI is a significant negative prognostic pointer for survival with MERS and SARS. Additional investigations are required to disclose the straight effects of MERS-CoV and SARS-CoV on renal complications. Furthermore, the prevalence of kidney disorders in patients with COVID19 more frequent, and this virus can directly penetrate human renal cells and is related to greater morbidity and mortality. Besides, improvement of eGFR would enhance the survival of COVID19 infected patients who have ARF. In general, regular and accurate monitoring of kidney functions in COVID19 subjects is necessary and can lead to early recognition of kidney impairments, and also help in applying the ideal management considerations and declining the risk of unwanted drug reactions and may help to decrease mortality of COVID19 infected patients.

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Figure Legend

Figure 1. Binding covid19 to ACE2 leads to suppression of ACE2 activity following augmented ACE2 shedding (via hyperactivation of ADAM17) and ACE2 down expression (via membrane fusion and virus entry into infected cells). It was hypnotized ACE1/ ACE2 imbalance and augmented Ang II/ AT1 signaling besides in attenuate Ang (1–7)/Mas signaling pathway. Augmentation in Ang II/AT1R axis triggers servals pathways including PI3K/Akt, JAK/STAT, ERK/MAPK which leads to overexpression of inflammatory factors, HIF-1, ROS, fibrosis factors. On the other hand, direct COVID-19 invasion leads to tubular epithelial and podocytes damages. Altogether mentioned factors and changes result in acute tubular necrosis, interstitial inflammation, podocyte injury, microangiopathy, and hypercoagulation to result in organ injury and AKI associated with COVID-19.

Table1: A comprehensive overview of coronavirus family characterization in settling of prevalence, kidney involvement rate, involved cellular receptors, and type of targeted kidney cells.

Coronaviruses	Type of outbreak	Prevalence AKI (%)	Kidney involvement associated mortality (%)	Cellular Receptor	Cells involved
SARS	Epidemic	5-15	60-90	ACE-II	Tubular cells
MERS	Epidemic	5-15	60-90	Dpp-4	Tubular cells
COVID19	Pandemic	20-40	20-50	ACE-II	Tubular cells and podocytes

SARS: *severe acute respiratory syndrome****; MERS:*** *middle east respiratory syndrome****; AKI:*** *acute kidney injury****; ACE:*** *angiotensin-converting enzyme****; Dpp4:*** *Dipeptidyl-peptidase 4*