Can cilia provide an entry gateway for SARS-CoV-2 to human ciliated cells?

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Abstract

A worldwide coronavirus pandemic is in full swing and, at the time of writing, there are only few treatments that have been successful in clinical trials, but no effective antiviral treatment has been approved. Because of its lethality, it is important to understand the current strain’s effects and mechanisms not only in the respiratory system but also in other affected organ systems as well. Past coronavirus outbreaks caused by SARS-CoV and MERS-CoV inflicted life-threatening acute kidney injuries (AKI) on their hosts leading to significant mortality rates, which went somewhat overlooked in the face of the severe respiratory effects. Recent evidence has emphasized renal involvement in SARS-CoV-2, stressing that kidneys are damaged in patients with COVID-19. The mechanism by which this virus infects AKI is still unclear, but evidence from other coronavirus strains may hold some clues. Two theories exist for the proposed mechanism of AKI: 1) the AKI is a secondary effect to reduced blood and oxygen levels causing hyperinflammation and 2) the AKI is due to cytotoxic effects. Kidneys express angiotensin-converting enzyme-2 (ACE2), the confirmed SARS-CoV-2 target receptor as well as collectrin, an ACE2 homologue that localizes to the primary cilium, an organelle historically targeted by coronaviruses. Although the available literature suggests that kidney damage is leading to higher mortality rates in patients with COVID-19, especially in those with preexisting kidney and cardiovascular diseases, the pathogenesis of COVID-19 is still being investigated. Here, we present brief literature review supporting our proposed hypothesis of a possible link between SARS-CoV-2 cellular infection and cilia.

ACE2; cilia; coronavirus; COVID-19

INTRODUCTION

In December 2019, China alerted the rest of the world of the existence of widespread and highly contagious human respiratory illness that was spreading rapidly among its population. This illness that was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was later dubbed Coronavirus Disease 2019 (COVID-19). SARS-CoV-2 belongs to the same family of viruses as those that caused the previous pandemics; severe acute respiratory syndrome coronavirus (SARS-CoV) originating from Guangdong, China in 2002, and Middle East respiratory syndrome coronavirus (MERS-CoV) originating from the Middle East in 2012 (1). The ongoing SARS-CoV-2 pandemic is a global health crisis that has high fatality rates and has taken a large social and economic toll worldwide. Based on currently available scientific literature, clinical expertise, and epidemiological studies, older adults and those with serious preexisting medical conditions are at higher risk for severe complications and face an increased mortality rate from SARS-CoV-2. Preexisting medical conditions that put patients with SARS-CoV-2 at higher risk include chronic lung disease, diabetes, liver disease, cardiovascular diseases including hypertension, and chronic kidney disease. Furthermore, healthy individuals, including young and middle-aged adults who contract the coronavirus may be infected equally regardless of their sex, race, and age. The Centers for Disease Control and Prevention (CDC) has identified African Americans as having increased risk of COVID-19-associated mortality mainly due to limited access to healthcare and related social determinants of health. A recent study found that COVID-19 mortality rates were generally higher in areas that had higher African American populations, particularly in the northeast United States (2). In addition, recent findings suggest higher mortality rate and greater disease severity in males than in females (3). Several factors may be contributing to this sex disparity in patients infected with COVID-19, including angiotensin-converting enzyme-2 (ACE2) expression levels, immunological, and behavioral and social differences between males and females (3, 4). To further complicate the matters, both asymptomatic and symptomatic cases have been reported. Common symptoms mimic those associated with the flu such as fever, cough, and fatigue; however, the presence of anosmia, minimal mucus production (dry-cough), and the specific order by which the symptoms present themselves aid in distinguishing COVID-19 from the standard flu. In addition to the respiratory distress that SARS-CoV-2 causes, kidney involvement is...
common in COVID-19 cases, with more than 40% of patients showing abnormal proteinuria (5). The mortality rate in patients with acute kidney injury (AKI) is three times higher than those without AKI (6). Clinical reports from China have shown that among patients with COVID-19, ~7% have AKI complications and up to 25% of critically ill patients have shown kidney comorbidities including kidney failure (7). In a clinical study in New York, 36.6% of patients experienced AKI, with a higher proportion in ventilated patients (89.7%) compared with nonventilated patients (21.7%) (8). Furthermore, kidney autopsy samples from patients who have died of coronavirus showed the presence of SARS-CoV-2 in glomerular, epithelial, endothelial, and tubular cells (9), providing clear evidence that SARS-CoV-2 directly invades kidneys.

**Coronavirus Structure and Life Cycle**

SARS-CoV-2, like other coronaviruses, consists of a single-stranded RNA that is enveloped in a spherical particle with spike-like projections on its surface. Its structure also includes 25 proteins that allow for the attachment to human cells and subsequent infection (10, 11). Coronaviruses (CoVs) generally, and SARS-CoV-2 specifically, house four main structural proteins embedded on their surfaces which are essential for replication of the virus (12, 13): 1) spike glycoprotein trimer (S) is involved in the early stages of infection where it mediates virus-receptor binding, entry into host cell, and induces host cell immune responses (10, 12). (S) has three segments: an ectodomain, a single-pass transmembrane anchor, and a short intracellular tail (12, 13) and two subunits, S1 and S2, that are responsible for receptor binding and membrane fusion respectively (14); 2) membrane protein (M) and 3) envelope small membrane protein pentamer (E) are both involved in virus assembly; and 4) nucleocapsid (N) where the genome is packed (12). The remaining 21 proteins encoded by the SARS-CoV-2 genome consist of open reading frames (ORF) and nonstructural proteins, both of which function to support virus survival and RNA-dependent RNA polymerase (Fig. 1) (10, 15).

According to previous research on the 2002 outbreak of SARS-CoV, the spikes located on the coronavirus’ surface bind to angiotensin-converting enzyme-2 (ACE2), thereby prompting studies to look for similar binding properties for the novel SARS-CoV-2 (16). Recent studies have confirmed this hypothesis, demonstrating that the binding affinity of

![Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) structure and proteins. Used with permission from Ref. 10.](image-url)
SARS-CoV-2 for ACE2 is 10–20 times higher than SARS-CoV (16). SARS-CoV-2 binding and subsequent entry into human cells relies on ACE2 and type II transmembrane serine proteases (TMPRSS2) that activate virus-receptor interactions (17). These interactions begin with the attachment of the S1 subunit of the viral spike protein to the receptor binding domain on ACE2. TMPRSS2 on the host cell is responsible for cleaving the S1 domain on the virus’ surface, thus exposing the S2 subunit responsible for membrane fusion between the virus and the human host cell (15, 17). From there, membrane fusion can follow two distinct paths, fusion at the plasma membrane (early pathway) or at the endosomal membrane (late pathway), a process driven and activated by chance interactions with specific proteases. Interactions with TMPRSS2 is believed to trigger the early fusion pathway; however, interactions with other proteases such as Furin, which cleaves the spike protein at a different location than TMPRSS2 and removes the S2 subunit, redirects viral entry to an endosomal-mediated mechanisms, highlighting the flexibility and adaptability of SARS-CoV2 (18). The endosomal pathway for viral entry has been extensively studied and is considered to be particularly important as inhibitors targeting the endocytic pathway appear to have therapeutic potential in the treatment of COVID-19 (19). Although evidence suggests that SARS-CoV, MERS-CoV, and SARS-CoV-2 use two separate entry mechanisms, cellular entry of coronaviruses in general can vary between viruses and host cell type; when looking at the endocytic pathway specifically, viral entry can use clathrin and/or caveolae-dependent and -independent pathways. This highlights the adaptability of this class of viruses to different environments as well as our need to better understand the mechanisms governing coronaviruses infection (20–22). The virus will gradually release its genomic material, mRNA, that is ready to be translated and then replicated within the host cell. The resulting structural proteins are transported to the endoplasmic reticulum (ER) and the Golgi where the components are assembled creating mature virions. From the Golgi, the virions are packaged into vesicles to be transported to and released at the cell surface (23) (Fig. 2).

Figure 2. General depiction of coronavirus life cycle. The steps in the coronavirus lifecycle are 1) binding of the virion to the cell via the S1 spike protein receptor interaction; 2) proteolytic cleavage of S protein into S1 and S2, followed by fusion of cellular and viral membranes and release of viral genome; 3) viral genomic RNA translation into replicase; 4) viral RNA synthesis; 5) viral structural proteins are translated; 6) moved into the endoplasmic reticulum (ER); 7) then into the Golgi-ER compartment and assembly of virions; 8) virions bud from Golgi-ER compartment; and 9) leave cell via exocytic pathway (23, 24). Used with permission from Ref. 25.

**CORONAVIRUSES AND CILIA INTERACTIONS**

Human coronaviruses, in general, are known to cause the loss of cilia from ciliated cells (26). Cilia are hair-like projections that function as sensory organelles and exist on almost every eukaryotic cell. There are two classes of cilia: motile and nonmotile, and both consist of a microtubule-based cytoskeleton called an axoneme (27). Variations in axonemal components differentiate the primary nonmotile cilia from the motile ones (Fig. 3) (29). There are various kinds of motile cilia; Multicilia have a $9 + 2$ structure containing a central pair of microtubules and dynein motor proteins giving rise to their wave-like motion. The major function of multiple motile cilia is to aid in fluid movement and mucus clearance (30). Nonmotile primary cilia lack a central pair of...
multiciliated human airway epithelial cell cultures (38). Coronaviruses have been proven to replicate and thrive within cultures of ciliated cells. This has led researchers to speculate that through cilia, coronaviruses have an advantageous form for cell entry (39–42). A recent study reported a "robust" localization of ACE2 in ciliated epithelial cells of the respiratory system, in pulmonary motile cilia, and within the primary cilia of kidney IMCD3 cells (Fig. 4). This might likely represent the initial or early subcellular site of SARS-CoV-2 viral entry during host respiratory, pulmonary, and kidney transmission (47). To further support our proposed hypothesis that the cilia could be the initial or early subcellular sites of SARS-CoV-2 entry, two recently published reports demonstrated that the SARS-CoV-2 antigen was clearly visualized in the ciliated cells of SARS-CoV-2-infected cynomolgus macaques and infected human coronavirus HKU1 (HCoV-HKU1), which was notoriously difficult to propagate in a laboratory, has been proven to replicate and thrive within cultures of multiciliated human airway epithelial cell cultures (38). Although HCoV-HKU1 has not been shown to enter cells through cilia, coronaviruses have an affinity for ciliary receptors in general, and this has led researchers to speculate that other more aggressive strains enter through ciliary receptors. Unfortunately, due to a lack of clinical interest in coronaviruses, until very recently, the exact ciliary receptors targeted by different viral strains remain relatively unknown. Some exceptions to this are ACE2, dipeptidyl peptidase-4 receptors (DPP4), and human aminopeptidase N, all of which are targeted by multiple human coronaviruses for cell entry (39–43). ACE2 and DPP4 receptors are found in both primary and multicilia present on various cell types (44–46).

Cilia as a Possible Means for SARS-CoV-2 Entry and Pathogenesis

In the current environment, the world is focused on creating an effective treatment option to battle the SARS-CoV-2 pandemic. Infection mechanisms of viruses have been studied for a century so current research is focused on how to stop SARS-CoV-2 specifically, not necessarily nuanced alternative perspectives in possible host cell entry sites, rightfully so. However, a potentially important element in understanding the pathogenesis of SARS-CoV-2 may have been overlooked. As stated, it is known that coronaviruses can cause a loss of cilia, impede motility functions, and mature virosomes have been shown to be trapped within motile cilia, but this evidence has mostly been investigated within the context of the respiratory system and pulmonary motile cilia or olfactory cilia. The multisystem and multiorgan symptoms observed in COVID-19 raise interesting questions with one explanation being a cilium-dependent entry-point or a cilium-mediated pathogenesis.

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bronchial cells ex vivo (48, 49). The related SARS-CoV has also been observed in the cilia of the airway (37). In addition, TMPRSS2 is known to be widely expressed in a number of cells and tissues but is also prominently expressed in the distal convoluted tubules, collecting duct, and the papillary epithelium of the kidneys (50). Although membrane fusion through ACE2 and TMPRSS2 is the implied preferred pathway, primary cilia also present an interesting target for the second suggested entry pathway of endocytosis. Due to the internal structure of primary cilia, cilia typically sit in a depressed or concaved area of the cell membrane; this area is known as the ciliary pocket and functions as an endocytic domain. As stated earlier, when SARS-CoV-2 is cleaved by other proteases than TMPRSS2, the entry pathway is redirected to an endocytic mechanism that can be mediated by clathrin. The clathrin pocket is enriched with clathrin coated pits making it highly significant for both endo and exocytosis (51, 52) and making cilia a potential two-way street for both viral entry and exit from the cell. Taken together, these data indicate that the cilia contain the necessary molecular components to enable cellular entry of SARS-CoV-2 and hence, collectively support a model in which SARS-CoV-2 first binds ACE2 present in the cilia of the upper airway or the kidney collecting duct cells before entry into ciliated epithelial cells (Fig. 5).

Currently, there is no consensus on whether viral binding to the cilia impacts cilia function. There is some evidence to suggest that in response to some coronavirus infections, a deciliation occurs, the extent of which is unknown and studies from nasal olfactory/upper respiratory cilia imply this deciliation is delayed and temporary, occurring at 3 days postinfection and returning to normal several days after recovery (26). However, taking a broad look at the reported symptoms and pathology of COVID-19 infection, primary cilia dysfunction may provide a commonality that links the diverse symptoms and severity seen in patients, and a research target to better understand the infection. Notably, primary cilia have been connected to immune system cells. This is depicted in studies demonstrating the repurposing of components of the ciliary machinery for the assembly and function of the immunological synapse as well as several studies describing the mechanisms of cilia regulation by immune reaction and the physiological relevance of cilia in regulating proliferation and differentiation of skin stroma cells. Primary cilia are also involved in several immune responses including inflammation, one of the predominant issues patients with COVID-19 face (53–58). The immune system may also impact primary cilia function as several cytokines have been shown to permanently lengthen primary cilia (59). More severe COVID-19 infections are characterized by the “cytokine storm,” a massive proinflammatory response, which is believed to result in acute respiratory distress syndrome and multiorgan dysfunction/failure (60).

SARS-CoV-2 is associated with kidney dysfunction and injury

SARS-CoV-2 has a growing list of target organs, among which are obviously the lungs, and less obviously the heart and kidneys. SARS-CoV-2’s adverse or damaging effects on the kidneys are just starting to gain clinical attention through several warnings from hospitals around the world. Elevated troponin, a common biomarker used for cardiovascular disease that is also elevated in patients with end-stage renal disease regardless of notable heart defects, has been reported in multiple patients with SARS-CoV-2 (61–63). In addition, the presence of kidney dysfunction and AKI among patients with the virus is becoming a common occurrence. An observational study in a New Orleans hospital reported that among the 644 patients with a confirmed diagnosis, 161 patients (28%) had AKI with a mortality rate of 50%. Common manifestations of kidney dysfunction were hyperkalemia, hyponatremia, high baseline values for serum ferritin and D-dimer levels. The reported increase in the baseline of inflammatory markers in these infected patients suggests that the cytokine release effects from the virus and the incidence of AKI are related (64). A cohort study of 193 laboratory-confirmed infected patients, 128 nonsevere cases and 65 severe cases, found that many patients had various forms of kidney dysfunction upon hospital admission that worsened over time. The kidney dysfunctions manifested as proteinuria (44%), hematuria (26.9%), elevated blood urea nitrogen
(BUN) (14.1%), and elevated serum creatinine (15.5%), along with high uric acid and elevated d-dimer levels; using univariate Cox regression analysis, these were all shown to be associated with mortality in patients with SARS-CoV-2. The analysis also reported that patients with SARS-CoV-2 who developed AKI had a significantly higher mortality risk than those without AKI (65). A second cohort study investigated abnormal urinalysis and kidney dysfunction in hospitalized patients with SARS-CoV-2 over the course of 20 days. Among 710 laboratory-confirmed infected patients, AKI occurred in 3.2% patients; however, it was found that 44% of patients had proteinuria, 26.9% had hematuria, 15.5% had elevated serum creatinine, and 14.1% had elevated BUN levels. Kaplan–Meier analysis and Cox proportional hazard regression showed that patients with kidney damage have a higher risk for hospital mortality (66). This suggests that while AKI significantly contributes to a patient’s mortality risk, kidney malfunction, at any level, plays a prominent role in pathogenesis and prognosis. This becomes even more relevant as an estimated 850 million patients currently live with renal diseases, which is double the prevalence of diabetes and 20 times more prevalent than cancer worldwide. As the virus continues to infect people, a growing list of studies confirms reports that patients with kidney impairment are at a significantly higher chance of mortality from SARS-CoV-2.

There are several reasons why SARS-CoV-2 may damage the kidneys. There is an argument that the kidneys are a casualty of significantly impaired lung function and viral replication in the respiratory tract in that a lack of oxygen due to lung damage is known to have deleterious effects on kidney function. The intense inflammatory response SARS-CoV-2 elicits can cause damage to healthy tissues in a variety of organs including kidneys, and blood clots in the kidneys caused by an increase in coagulation factors can impair the filter-like function of the kidneys (67–69). An equally valid alternative theory is that SARS-CoV-2 directly targets and invades kidney cells (70), potentially via the primary cilia. With evidence supporting both sides of the argument, it is beginning to look as though the kidneys are both passive and active participants in COVID-19 infection. To complicate the matters further, it is still not clear whether SARS-CoV-2 can bind and enter through other receptors. For example, collectrin is involved in vesicle transport and membrane fusion and is homologous to ACE2 (71). Little is known about the function of collectrin but originally, it was discovered in the renal cortical membrane as a binding partner to amino acid transporters where it mediated homo-/heterodimerization of various proteins (72). Studies report SARS-CoV-2 does not bind to the collectrin domain on ACE2 (73). However, collectrin has been shown to mediate the heterodimerization

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**Figure 5.** Proposed coronavirus entry into cells through primary cilia pathway. Detailing entry through endocytosis in the ciliary pocket as well as exocytosis of the mature virions through ciliary mechanisms. Created with BioRender.com.
of ACE2 and neutral amino acid transporter B^0\text{AT}1. This complex provides a site for the receptor binding domain (RBD) of SARS-CoV-2 S1 to interact with this complex forming the RBD-ACE2-B^0\text{AT}1 ternary complex (73), thus suggesting that collectrin-mediated heterodimerization can create unknown SARS-CoV-2 receptor binding domains with proteins other than ACE2 (73–75). Collectrin has also been shown to localize to primary cilia in renal collecting ducts (76) leading to question whether there are additional binding sites for SARS-CoV-2, unique to the kidney, that are contributing to the renal dysfunction and failure observed in patients with severe COVID-19. It is intriguing to speculate how SARS-CoV-2 binding to ACE2 receptors in the primary cilia can lead to the renal manifestations of patients with COVID-19 such as AKI and others. Dysfunction in ciliary signaling and ciliary structure has been linked to many cardiovascular and kidney diseases such as hypertension, control of the renin angiotensin aldosterone system (RAAS) (77), nephropathies, renal cystic dysplasia, and renal cell carcinoma (RCC) (12). Primary cilia contribute to the regulation of the cell cycle and protein homeostasis, by acting on the ubiquitin-proteasome system, autophagy, and mechanistic target of rapamycin (mTOR) signaling. Moreover, primary cilia are associated with essential signaling pathways, such as Hedgehog, Wnt, and platelet-derived growth factor (PDGF). This raises questions as to whether SARS-CoV-2, through interaction with ACE2 or collectrin, might interfere with ciliary function. Could viral binding to ciliary ACE2 cause a disruption in ciliary signaling and structure, potentially linked to the renal manifestations often observed in patients with COVID-19? Could the cilia dysfunction also play a role in kidney failure in patients with severe COVID-19? More studies are needed to further explore these questions.

There are similarities in renal manifestations of SARS-CoV-2 compared with other coronaviruses, especially MERS-CoV. The cellular receptor for MERS, DPP4, is highly expressed in the kidneys and is likely to be directly affected by the virus. A cohort study in Saudi Arabia reported 42.9% of patients with MERS developed AKI throughout their infection (78). Urine was used to detect the virus, which is an indication of renal dysfunction, and patients also experienced higher albumin to creatinine ratios (79). In addition, histopathological studies of postmortem specimens from deceased patients with MERS showed the presence of MERS-CoV virus in patients’ renal tissues (71). SARS-CoV, on the other hand, is not as common and may be less of a direct effect. In patients with SARS-CoV, acute renal failure was a latent effect (emerging after 7–20 days of infection) and only in 5%–15% of patients, with highest incidence in elderly patients with comorbidities. However, among the patients with renal failure, the morbidity is higher in patients with SARS-CoV, with a mortality rate of ~90% (80). Renal impairment is a noticeable complication among influenza viruses, such as hemagglutinin 1 and neuraminidase 1 (H1N1) virus that caused the 2009 Influenza A pandemic. A cohort study in Spain among 661 infected patients, 18% of them developed AKI (81). Overall, the renal effects of SARS-CoV-2 have more similarities with MERS-CoV compared with SARS-CoV.

# CONCLUSIONS

Historically, apart from SARS-CoV, human coronaviruses are not well understood. This is partly due to the now incredibly mistaken belief that they are only involved in mild respiratory tract infections and are not worth the time and effort to study. SARS-CoV-2 has been found to cause severe respiratory, renal, and cardiovascular damage, and likely wreaks havoc elsewhere. Understanding its mechanisms is the first step to developing treatments. Kidney cells express ACE2 and collectrin; the former is a confirmed target for both SARS-CoV and SARS-CoV-2, whereas the latter is a possible target for SARS-CoV-2 due to its localization to cilia, and its homology to ACE2. The recent outbreaks of coronaviruses are more than likely a prelude to a “coronavirus season,” much like the normalized “flu seasons.” This is leading to a rather severe risk for patients with ciliopathies, cardiovascular diseases, and renal diseases. Still, any additional target organs and target receptors of SARS-CoV-2 remain a mystery and require further research. A high pathogenicity is to be expected with all coronaviruses, and for SARS-CoV-2 especially, the possibility of the development of a recombinant virus variant is very high.

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# DISCLAIMER

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# DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

# AUTHOR CONTRIBUTIONS

R.B., H.S., and S.L. prepared figures; R.B., H.S., S.L., A.A., and W.A.A. drafted manuscript; H.S., S.L., K.F., and W.A.A. edited and revised manuscript; W.A.A. approved final version of manuscript.

# REFERENCES

1. Xu RH, He JF, Evans MR, Peng GW, Field HE, Yu DW, Lee CK, Luo HM, Lin WS, Lin P, Li LH, Liang WJ, Lin JY, Schnurr A. Epidemiologic clues to SARS origin in China. Emerg Infect Dis 10: 1030–1037, 2004. doi:10.3201/eid1006.030852.
2. Anaele BI, Doran C, McIntire R. Visualizing COVID-19 mortality rates and African-American populations in the USA and Pennsylvania. J Racial Ethn Health Disparities. In press. doi:10.1007/s40615-020-00897-2.
3. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, Rosser EC, Webb K, Deakin CT. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and
ITU admission. Nat Commun 11: 6317, 2020. doi:10.1038/s41467-020-19746-1.

Bwiré GM. Coronavirus: why men are more vulnerable to Covid-19 than women?. SN Compr Clin Med 2: 874–876, 2020. doi:10.1007/s42399-020-00341-w.

Patel SK, Singh R, Rana J, Tiwari R, Natesan S, Harapan H, Arteaga-Livias K, Bonilla-Aldana DK, Rodriguez-Morales AJ, Dharma K. The kidney and COVID-19 patients—important considerations. Travel Med Infect Dis 37: 101831, 2020. doi:10.1016/j.tmaid.2020.101831.

Soleimani M. Acute kidney injury in SARS-CoV-2 infection: direct effect of virus on kidney proximal tubule cells. Int J Mol Sci 21: 3275, 2020. doi:10.3390/ijms21032755.

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 46: 1114–1116, 2020. doi:10.1007/s00134-020-06026-1.

Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazan AD, Fishbane S, Jhaveri KD, Northwell C-RC, Northwell NC-RC, Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 98: 209–218, 2020. doi:10.1016/j.kint.2020.05.006.

Puelles VG, Lutgeheym M, Lindenheym MT, Sperahke JP, Wong MN, Alistor L, Chilla S, Heinemann A, Wanner N, Liu S, Braun F, Lu S, Pfefferle S, Schroder AS, Eder C, Gross O, Glatzel M, Wichmann D, Viech T, Kluge S, Pueschel K, Aepfelbacher M, Huber TB. Multigorgan and renal tropism of SARS-CoV-2. N Engl J Med 383: 590–592, 2020. doi:10.1056/NEJMc2101400.

Parks JM, Smith JH. How to discover antiviral drugs quickly. N Engl J Med 382: 2261–2264, 2020. doi:10.1056/NEJMcb2002042.

Gunzberg WJ. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res 81: 537–540, 2020. doi:10.1002/ddr.25656.

Santoni M, Piva F, Ciudadamore A, Giulietti M, Battelli N, Montironi R, Cosmai L, Porta C. Exploring the spectrum of kidney ciliopathies. Diagnostics (Basel) 10: 1099, 2020. doi:10.3390/diagnostics10120199.

Torritoci MA, Veesler D. Structural insights into coronavirus entry. Adv Virus Res 105: 93–116, 2019. doi:10.1016/bs.avir.2018.09.002.

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 181: 281–292, 2020. [Erratum in Cell 183: 1735, 2020. doi:10.1016/j.cell.2020.02.058.

Bian C, Zhang X, Cai X, Zhang L, Chen Z, Zha Y, Xu Y, Xu K, Lu W, Yan L, Yuan J, Feng J, Hao P, Wang G, Zhao G, Liu G, Zhu X, Shen H, Zheng B, Shen B, Sun B. Conserved amino acids W423 and N424 in receptor-binding domain of SARS-CoV-2 are potential targets for therapeutic monoclonal antibody. Virology 438: 39–46, 2009. doi:10.1016/j.virol.2008.08.029.

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367: 1260–1263, 2020. doi:10.1126/science.abb2507.

Astduti FY. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diabetes Metab Syndr 14: 407–412, 2020. doi:10.1016/j.dsx.2020.04.020.

Tang T, Bidon M, Jaimes JA, Whittaker GR, Daniel S. Coronavirus membrane fusion mechanism offers a potential target for antiviral development. Antiviral Res 178: 104792, 2020. doi:10.1016/j.antiviral.2020.104792.

Yang N, Shen HM. Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19. Int J Biol Sci 16: 2172, 2020. doi:10.7150/ijbs.45498.

Giebog OO. Understanding SARS-CoV-2 endocytosis for COVID-19 drug repurposing. FEBS J 287: 3664–3671, 2020. doi:10.1111/febs.15369.

Szczechanski A, Owczarek K, Milewska A, Baster Z, Rajfur Z, Mitchell JA, Pyrc K. Canine respiratory coronavirus employs caveolin-1-mediated pathway for internalization to HRT-1B cells. Vet Res 49: 55, 2018. doi:10.1186/s13567-018-0551-9.

Wang H, Yang P, Liu K, Gao F, Zhang Y, Zhang G, Jiang C. SARS coronavirus entry into host cells through a novel clathrin- and caveolar-independent endocytic pathway. Cell Res 28: 290–301, 2008. doi:10.1038/cr.2008.15.
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dysfunction in pulmonary arterial hypertension: loss of cilia length regulation upon cytokine stimulation. "Pulm Circ" 8: 2045894018754622, 2018. doi:10.1177/2045894018754629.

Yuki K, Fujiy M, Koutsogiannaki S. COVID-19 pathophysiology: a review. "Clin Immunol" 215: 108427, 2020. doi:10.1016/j.clim.2019.108427.

Driggin E, Madhavan MV, Bikdeli B, Chuchl T, Laracy J, Blondi-Zocci G, Brown TS, Der N Viggothizzi C, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM, Parkih SA. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. "J Am Coll Cardiol" 75: 2352–2371, 2020. doi:10.1016/j.jacc.2020.03.031.

Clerkin KJ, Fried RA, Rakelher J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burdoff D, Kumariah R, Dabani L, Schwartz A, Uriel N. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. "Circulation" 141: 1648–1655, 2020. doi:10.1161/CIRCULATIONAHA.120.046941.

Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Panish M. COVID-19 infection in kidney transplant recipients. "Kidney Int" 97: 1076–1082, 2020. doi:10.1016/j.kint.2020.03.018.

Mohamed MMB, Lukitsch I, Torres-Oritz AE, Faller JB, Varghese V, Hernandez-Arroyo C, Algood M, Le DD, VR. Jelvez JCQ. Acute kidney injury associated with coronavirus disease 2019 in urban New Orleans. "Kidney360" 1: 614–622, 2020. doi:10.34067/KID.00026520.

Li Z, Wu M, Yao J, Guo J, Liao X, Song S, LI J, Duan G, Zhou Y, Wu X, Zhou Z, Wang T, Hu M, Chen X, Fu Y, Le I, Dong H, Xu C, Hu Y, Han M, Zhou Y, Jia H, Chen X, Yan J. Caution on kidney dysfunction in COVID-19 patients. medRxiv. 2020. doi:10.1101/2020.02.08.20021212.

Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. "Kidney Int" 97: 829–838, 2020. doi:10.1016/j.kint.2020.03.005.

Vinayagam S, Sattu K. SARS-CoV-2 and coagulation disorders in different organs. "Life Sci" 260: 118431, 2020. doi:10.1016/j.lfs.2020.118431.

Loganathan S, Kuppasamy M, Wankhar W, Gurugubelli KR, Mahadevappa VH, Lepcha L, Choudhary AK. Angiotensin-converting enzyme 2 (ACE2): COVID-19 gate way to multiple organ failure syndromes. "Respir Physiol Neurobiol" 283: 103548, 2021. doi:10.1016/j.respr.2021.103548.

Hansell P, Welch WJ, Blantz RC, Palm F. Determinants of kidney oxygen consumption and their relationship to tissue oxygen tension in diabetes and hypertension. "Clin Exp Pharmacol Physiol" 40: 123–137, 2013. doi:10.1111/1440-1618.12034.

Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2? "Am J Physiol Renal Physiol" 318: F4154–F4162, 2020. doi:10.1152/ajprenal.00620.2020.

Zhang Y, Wada J, Collectin, a homologue of ACE2, its transcriptional control and functional perspectives. "Biochim Biophys Acta Gen Comp" 1836: 1–5, 2007. doi:10.1016/j.bbagrm.2007.08.016.

Zhang H, Wada J, Hida K, Tsuchiyama Y, Hiragushi K, Shikata K, Wang H, Lin S, Kanwar YS, Makino H. Collectin, a collecting duct-specific transmembrane glycoprotein, is a novel homolog of ACE2 and is developmentally regulated in embryonic kidneys. "J Biol Chem" 276: 17132–17139, 2001. doi:10.1074/jbc.M100722200.

Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. "Science" 367: 1444–1448, 2020. doi:10.1126/science.abd12762.

Kowalczyk S, Broer A, Tietze N, Vanslambrouck J, Rasko JE, Broer A. A protein complex in the brush-border membrane explains a Hartnup disorder allele. "FASEB J" 22: 2880–2887, 2008. doi:10.1096/fasebj.08-107300.

Fukui K, Yang Q, Cao Y, Takahashi N, Hatakeyama H, Wang H, Wada J, Zhang Y, Marselli L, Nammo T, Yongeda K, Onishi M, Higashiyama S, Matsuzawa Y, Gonzalez FJ, Weir GC, Kasai H, Shimomura I, Miyagawa J, Wollheim CB, Yamagata K. The HNF-1 target collectin controls insulin exocytosis by SNARE complex formation. "Cell Metab" 2: 373–384, 2005. doi:10.1016/j.cmet.2005.11.003.

Zhang Y, Wada J, Yasuhara A, Iseda I, Eguchi J, Fukui K, Yang Q, Yamagata K, Hiesberger T, Igarashi P, Zhang H, Wang H, Akagi S,
Kanwar YS, Makino H. The role for HNF-1beta-targeted collectrin in maintenance of primary cilia and cell polarity in collecting duct cells. PLoS One 2: e414, 2007. doi:10.1371/journal.pone.0000414.

77. Reho JJ, Guo DF, Morgan DA, Rahmouni K. Smooth muscle cell-specific disruption of the bbsome causes vascular dysfunction. Hypertension 74: 817–825, 2019. doi:10.1161/HYPERTENSIONAHA.119.13382.

78. Gerges HJ, Noureldine HA, Chedid G, Eldine MN, Abdallah DA, Chedid NF, Nour-Eldine W. SARS, MERS and COVID-19: clinical manifestations and organ-system complications: a mini review. Pathog Dis 78: ftaa033, 2020. doi:10.1093/femspd/ftaa033.

79. Gulati A, Pomeranz C, Qamar Z, Thomas S, Frisch D, George G, Summer R, DeSimone J, Sundaram B. A comprehensive review of manifestations of novel coronaviruses in the context of deadly COVID-19 global pandemic. Am J Med Sci 360: 5–34, 2020. doi:10.1016/j.amjms.2020.05.006.

80. Alsaad KO, Hajeer AH, Al Balwi M, Al Moaiqel M, Al Oudah N, Al Ajlan A, AlJohani S, Alsolamy S, Gmati GE, Balkhy H, Al-Jahdali HH, Baharoon SA, Arabi YM. Histopathology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection—clinicopathological and ultrastructural study. Histopathology 72: 516–524, 2018. doi:10.1111/his.13379.

81. Martin-Loeches I, Papiol E, Rodriguez A, Diaz E, Zaragoza R, Granada RM, Socias L, Bonastre J, Valverdu M, Pozo JC, Luque P, Julia-Narvaez JA, Cordero L, Albaya A, Seron D, Rello J; Group HNSW. Acute kidney injury in critical ill patients affected by influenza A (H1N1) virus infection. Crit Care 15: R66, 2011. doi:10.1186/cc10046.