

## Molecular Basis of Kidney Defects in COVID-19 Patients

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### Abstract

**Background:** Kidney damage is considered to be one of the risk factors for severity and mortality among COVID-19 patients. However, molecular nature of such observations remains unknown.

**Hypothesis:** Altered gene expressions due to infection and in chronic kidney disease could explain severity in COVID-19 with kidney defects.

**Methods:** We collected gene expression data from publicly available resources Gene Expression Omnibus CKD, Enrichr for deregulated genes in SARS-CoV infected cells *in vitro*, DisGeNET and others and carried out enrichment analysis using Enrichr.

**Result:** Number of common genes altered in chronic kidney disease (CKD) and SARS-CoV infected cells was 2834. Enrichment analysis revealed that biological processes related viral life cycle and growth, cytokines, immunity, interferon, inflammation, apoptosis, autophagy, oxidative stress and others were significantly enriched with common deregulated genes. Similarly, significantly enriched pathways related to viral and bacterial infections, immunity and inflammation, cell cycle, ubiquitin mediated proteolysis, signaling pathways like Relaxin signaling pathway, mTOR signaling pathway, IL-17 signaling pathway, NF-kappa B signaling pathway were enriched with the common deregulated genes. These processes and pathways are known to be related to kidney damage. DisGeNET terms enriched include and related to Dengue fever, chronic Hepatitis, measles, retroviridae infections, respiratory syncytial virus Infections and many others. Kidney dysfunction related terms ischemia of kidney, renal fibrosis and diabetic nephropathy.

**Conclusion:** Common deregulated genes in SARS-CoV infected cells and chronic kidney disease, as well as their enrichment with molecular processes and pathways relevant for viral pathogenesis and renal dysfunctions, could explain the severity of COVID-19 with kidney disease. This observation not only provides molecular relation of severity in COVID-19 with renal dysfunctions but might also help in the management and treatment targets for these cases.

### **Keywords**

COVID-19; kidney disease; comorbidity; enrichment analysis; biological processes and pathways

## **Introduction**

The global pandemic of novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) may cause severe disease in the elderly and those with comorbidities like hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular, cerebrovascular, liver, kidney, and gastrointestinal diseases and may cause pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction and death [1-8].

### **Renal function impairment in COVID-19 patients**

Renal involvement was seen in other strains of Coronavirus, Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) and Middle East Respiratory coronavirus (MERS-CoV) infection [9, 10]. Risk of acute kidney injury (AKI) was low (3-5%) in initial reports of COVID-19 [11] but reported as high as 15% in later analyses. The incidence increases (25-29%) with ICU admission [12, 13] and in those with underlying chronic kidney disease [14]. In COVID-19 patients with acute kidney injury (AKI), mortality increased to 25-50% [15-20]. Initially, it was believed that immunosuppressed condition like chronic kidney disease (CKD) may protect against cytokine storm, but later it was observed that CKD, particularly end-stage kidney disease (ESKD) increasing mortality to COVID-19.[18-21] It may be due to older age, depressed immunity and associated comorbidity like diabetes, hypertension, and cardiac diseases and unavoidable exposure to hospital environment in patients on hemodialysis [16]. Significant proportion of COVID-19 patients also had proteinuria and hematuria [22-27].

Renal histopathological analysis of 26 autopsy specimen showed 9 (35%) of COVID-19 patients had acute tubular injury with non-isometric vacuolization, 7 (27%) patients had presence of virus in renal tubular epithelium and podocytes. Some blood vessels were blocked with erythrocytes. Associated lesions like pigment cast, pyelonephritis and 2 had FSGS lesion with foot process effacement were observed [28]. Collapsing glomerulopathy with tuft collapse and overlying epithelial hyperplasia has been also been reported in COVID 19 patient [29].

SARS CoV-2, which affects lungs as primary organ, can cause renal injury by various ways like direct cytokine injury, organ crosstalk and systemic effects [30, 31]. SARS CoV-2 might also cause renal injury directly. Angiotensin-converting enzyme type 2 (ACE2) acts as receptor for

SARS CoV-2 is mainly observed in type II alveolar epithelial cells in lungs. ACE2 expression is also high in renal epithelial and bladder cells. Podocytes and proximal straight tubule can act as kidney host cells for infection and podocyte injury might be responsible for proteinuria seen in some cases [32]. Viral RNA has also been isolated from urine in COVID-19 patients. This observation supports viral tropism for kidney [25]. Electron microscopic examination further showed clusters of coronavirus particles with distinctive spikes in the tubular epithelium and podocytes. Immunostaining with SARS-CoV-2 nucleoprotein antibody was positive in tubules. This result shows that SARS-CoV-2 could directly enter into the kidney cells, even though the stage of the disease was unknown [28, 33].

Accumulative epidemiological evidences suggest that episodes of AKI and subsequent development or progression of CKD are associated. Severity of AKI and repeated episodes of AKI are associated with increased risk of CKD. Studies with animal models have provided evidence for a biological basis linking episodes of AKI with CKD [34]. Mitochondrial dysfunction, cell death, and inflammation are considered to be the underlying pathogenesis of AKI. Dysfunctions of these processes and pathways may lead to progressive chronic disease. Complex interconnections of these pathways are likely to cross-talk between the tubular epithelium, endothelium, and interstitial compartments (reviewed in Zuk and Bonventre [35]). Common changes in cytokine level and inflammation between AKI and CKD have been reviewed [36]. This observation indicates that at the molecular level, pathways altered in CKD and AKI could be similar. AKI and CKD observed among COVID-19 patients might thus have similar molecular changes altering different pathways.

#### **Altered expression of host genes in response to infection by SARS-CoV and SARS-CoV-2**

Once the virus enters into the host, it manipulates host machinery for replication and its survival against immune response of the host. Altered expression of host genes has been identified in response to diverse viral infections. Analysis of host transcriptional response to SARS-CoV-2 and other respiratory infections through *invitro*, *ex vivo* and *in vivo* model systems reveals that each virus deregulates many common genes for antiviral activity as well as unique transcriptional footprints of individual virus. Compared to the response to influenza A virus and respiratory syncytial virus, SARS-CoV-2 shows a different response that lacks robust induction of a subset of cytokines including the Type I, Type III interferon and numerous chemokine.

Taken together, these data suggest that the unique transcriptional signature of SARS-CoV-2 might be responsible for COVID-19 [37]. In SARS-CoV infected peripheral blood mononuclear cells, increased expression of cytokines and transcription regulators has been identified. Expressions of genes involve inactivation of macrophages and coagulation pathways were also increased [38]. Differential expression genes in interferon pathway between patients with acute respiratory distress syndrome (ARDS) and without ARDS have been identified [39]. During SARS-CoV infection in humans, deregulated cytokine and inflammatory response have been observed and correlated with pulmonary pathology. Levels of type I interferon and interferon stimulated genes (ISGs) were elevated in patients infected with SARS-CoV. IL-6 and IL-8 genes, as well as TNF- $\alpha$  and IL-1 $\beta$  genes, have also been associated with ARDS [40, 41]. In SARS-CoV infected monocyte cells, expression of interferon and related genes was decreased after 24h of infection. Expression of Toll-like genes was increased while expression of MyD88, TRIF-1 and SITPEC was decreased in same conditions. Expression of cytokine was increased and expression of TRAF4, TRAIL, TGF $\beta$ 2, Endoglin, IL-6R and IL-13 were decreased. Expression of chemokine, complement C3 (C3), PDGFRA and LTA4H was increased. Expression of genes associated with fibrosis was increased and expression of PROS1 (protein S), MMP2, SPON2, PLOD3, ADAMTS4 and TIMP3 was decreased [42]. Altered expression of many host genes has been reported after infection of SARS-CoV at different time points and catalogued in Enrichr at <https://amp.pharm.mssm.edu/Enrichr/> [43,44]. To summarize, expression of many genes associated with cytokine, chemokine and inflammation are altered in SARS-CoV infected cells. Similar result is also reported for cells expressing SARS-CoV-2 infected cells.

### **Interaction of viral protein coded by SARS-CoV and host protein**

Host protein-viral protein interactions for SARS-CoV are studied extensively and reviewed [45]. Interactions of host proteins with viral proteins are also predicted using P-HIPSTer (Pathogen-Host Interactome Prediction using STructurEsimilaRity) algorithm that exploits both sequence- and structure-based information to infer interactions between pathogen and human proteins. Interactions are catalogued in this database (<http://phipster.org/>) and catalogued at Enrichr at <https://amp.pharm.mssm.edu/Enrichr/> [43, 44]. Interactions of proteins coded by the new pandemic virus SARS-CoV-2 with the host proteins are not studied extensively [46-48].

### **Altered expression of genes in chronic kidney disease and acute kidney injury**

To identify the markers which potentially contribute to tubular cell damage and tubulointerstitial fibrosis in CKD, altered expressions of hundreds of genes have been identified. Functional classifications of the differentially expressed genes in CKD revealed that deregulated genes were associated with cell cycle, blood vessel morphogenesis, cardiac development, cell adhesion, erythropoietin pathway, inflammation mediated by IL-2 signaling, response to unfolded proteins and others. Expression of hepatitis A virus cellular receptor 1(HAVCR1) gene, also known as KIM-1, LCN2 gene, involves in transport of lipids, steroid hormones and retinoids and plays a role in innate immunity by limiting bacterial growth as a result of sequestering iron-containing siderophores and others were deregulated [49]. Differentially expressed genes from peripheral blood in advanced stage of CKD were enriched and associated with insulin-like growth factor activity, neuroactive receptor interaction, the complement system, lipoprotein metabolism and lipid transport. Genes were also associated ubiquitin pathway, cytoskeletal remodeling, the clathrin-coated endosomal pathway, T-cell receptor signaling and CD28 pathways, and many immune pathways [50]. Various processes and pathways like cytokine and interferon signaling, ubiquitination mediated proteasome degradation, activation of NFkB, cell cycle, infection, apoptosis, Wnt signaling, p53 dependent DNA damage response and others were enriched with deregulated genes in CKD [51].

Differential expressions of many genes like LCN2, CCL2, CCL20, CXCL2, EGR1, IGF1R,IL-8, IL-11, IL6ST, IL13RA1, IFI16, COL4A1, COL4A2, FN1, FGA, LEPR and others are identified in early kidney transplant with AKI. Differentially expressed genes are associated with interstitial inflammation, synthesis of extracellular matrix, increased cell migration and effects of TGFB1 [52, 53]

### **Knowledge gap**

Kidney damage is one of the risk factors for severity and mortality among COVID-19 patients; although the molecular nature of the risk is not fully known. Increased viral load and decreased clearance of the viruses have been observed among severe COVID-19 patients [54]. It is thus likely that when SARS-CoV-2 infects a person with renal abnormalities like AKI or CKD, viruses may grow aggressively or the clearance might be affected enhancing the severity. Alternately, modified biological processes and pathways in CKD or AKI and SARS-CoV-2

infected cells had similarity and might act synergistically to increase disease severity. Cross talk between kidney damage in AKI or CKD and lung injury has been observed. AKI or CKD affects the acute lung injury through systemic pro-inflammatory cytokines and mediated through heme oxygenase 1, HMOX1 [55, 56] or through modification of neutrophil and platelet functions [57]. Direct infection of SARS-CoV-2 kidney cells and inducing the damage could not be ruled out [28, 33]. Infection with SARS-CoV alters expression of hundreds of genes *in vitro*. Similarly, altered expressions of thousands of genes have been described in CKD. It is unknown whether deregulated genes in these 2 different conditions were similar or belong to similar biological processes and pathways.

## **Hypothesis**

Altered gene expressions due to infection and in chronic kidney disease could explain severity in COVID-19 with kidney defects

## **Material and Methods**

### **Data sources**

#### **Altered expression of genes in SARS-CoV infected cells in vitro**

Increased (up) and decreased (down) expression of host genes on infection with virus at different time points are downloaded from Gene Expression Omnibus (GEO) database, a public functional genomics data repository (<https://www.ncbi.nlm.nih.gov/geo/>) and catalogued in Enrichr at <https://amp.pharm.mssm.edu/Enrichr/> [43, 44]. We downloaded the data for SARS-CoV only. Detailed result is shown in the **Supplementary Tables S1A and S1B**.

#### **Altered expression of genes in chronic kidney disease**

There are several reports for altered expression of genes in CKD in different tissues. We reanalyzed the expression data reported in peripheral blood samples ([50] GEO ID GSE37171) and kidney biopsy samples ([49] GEO ID GSE66494). Detail of increased and decreased expression of genes in blood (**Supplementary Tables S2A and S2B**) and kidney tissue (**Supplementary Tables S3A and S3B**) are shown in the supplementary **Tables S2 and S3**. Summary of the result is shown in the **Table 1**.

**Table 1: Gene expression data for using microarray in chronic kidney disease using microarray**

<b>Diabetes</b>	<b>Source of tissue</b>	<b>No of control / No cases</b>	<b>Increased (I)/decreased(D) expression of genes</b>	<b>Reference (ID)</b>
CKD	Kidney biopsy	8/53	9257 (I)/2763 (D) Adjusted $p \leq 0.0544$	[49], GSE66494
CKD	PBMC	40/66	10826(I)/7538(D) Adjusted $p \leq 0.0544$	[50], GSE37171

### **Interaction of host proteins with SARS-CoV and SARS-CoV-2 coded proteins**

Interactions of host protein with SARS-CoV coded proteins are downloaded from Enrichr at <https://amp.pharm.mssm.edu/Enrichr/> [43, 44] and shown in Supplementary **Table S4A**. Interacting partners of SARS-CoV-2 coded proteins are taken from published result [46, 47] and shown in the Supplementary **Table S4B**.

### **Enrichment analysis**

Enrichment analysis for the genes was carried out using online facility at Enrichr at <https://amp.pharm.mssm.edu/Enrichr/> [43, 44]. Enrichr is an integrative web-based software application for analysis of a gene-set comparing with various gene-set libraries. Given an input list of genes, it provides enrichment for different libraries like Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, Gene Ontology (GO) terms for biological processes, DisGeNET, a discovery platform containing publicly available collections of genes and variants associated to human diseases.

We searched “Pubmed” (<https://www.ncbi.nlm.nih.gov/pubmed/>) for relevance of the genes associated with different biological processes and pathway. For comparison of different set of genes/proteins, we used an online facility at <http://bioinformatics.psb.ugent.be/webtools/Venn/>

## **Result**

### **Comparison of altered expression of genes in CKD and SARS-CoV infected cells *in vitro***

Kidney injury has been reported earlier for SARS-CoV infection [58]. SARS-CoV and closely related viruses SARS-CoV-2 have genomic sequence similarity (94.6% similar in amino acid



sequence and 80% similar in nucleotide sequence) [59]. These two viruses also have structural similarities of proteins coded by them [60], some of the symptoms in infected patients by two viruses are similar. Comorbidity with kidney abnormalities [9,10,58], diabetes and cardiovascular disease [61] in COVID-19 and earlier SARS-CoV infected patients are also similar. However, SARS-CoV and SARS-CoV-2 differed in their infectivity and mortality in infected patients [62]. Thus, we assumed that altered gene expression in SARS-CoV would be similar. Both CKD and AKI are risk factors for severity of COVID-19 (Table 1). Severity of AKI and repeated episodes of AKI are also associated with increased risk of CKD [34]. Thus we have used altered gene expression data in CKD in our analysis. Comparison of gene expression altered in SARS-CoV infected cells and deregulated genes in CKD in the same direction (increased and decreased), revealed that 2834 unique genes were common (**Table 2**). Detail result is shown in **Supplementary Table S5**. These genes separately might contribute to the pathogenesis viral infection or CKD.

**Table 2: Common genes altered in SARS-COV infected cells and CKD patients**

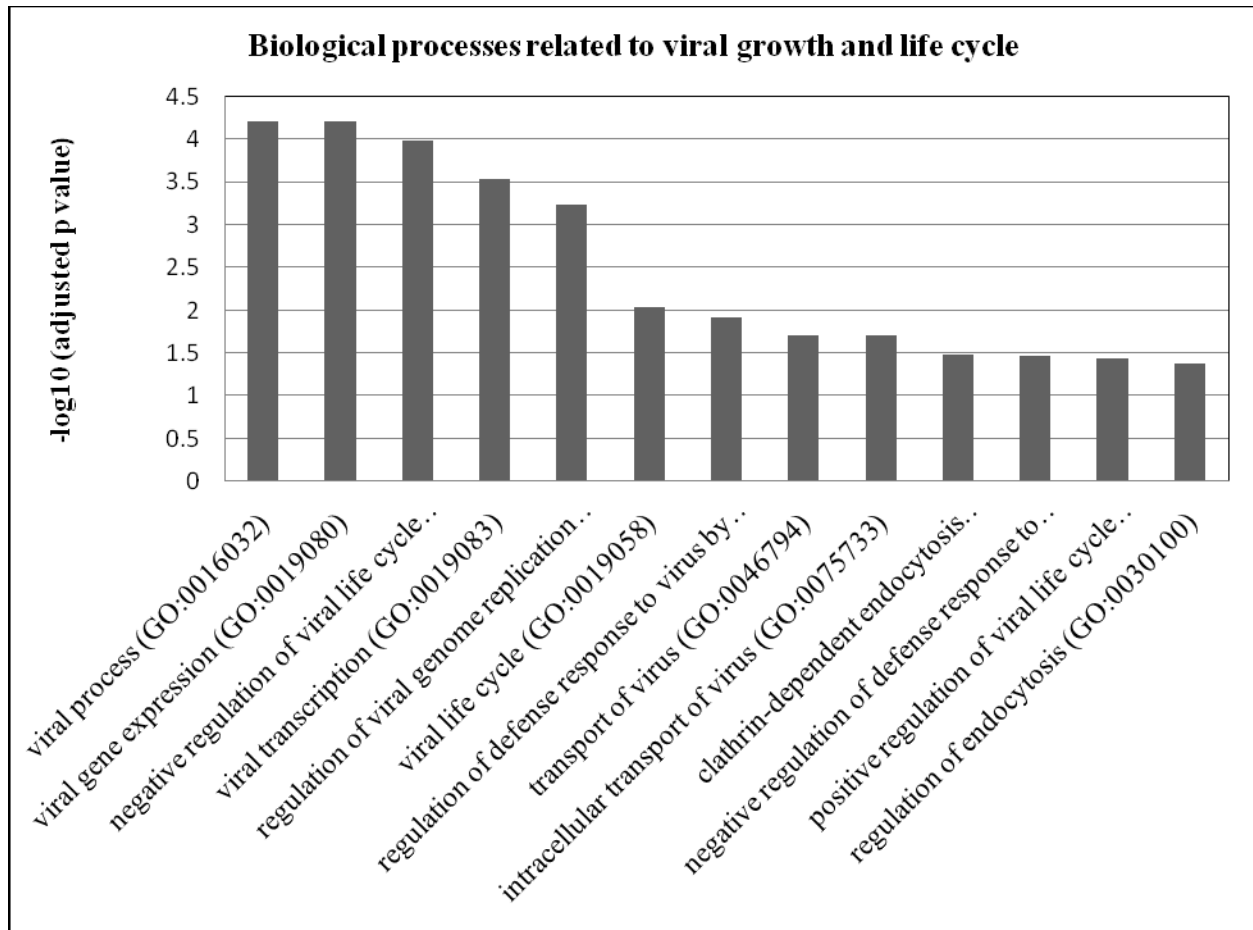
Condition	No of genes Increased/decreased in	No of genes increased/ decreased in Infected cells	Common genes in CKD and virus infected cells
CKD	PBMC (I):10826	Increased:3464	PBMC:1322
	Kidney (I):9275		Kidney:1768
	PBMC (D):10410	Decreased:694	PBMC:553
	Kidney (D):2769		Kidney:80

### **Enrichment analysis with common gene deregulated in viral infected cells and CKD**

We carried out enrichment analysis using Enrichedr for biological processes defined by Gene Ontology (GO), biological pathways as catalogued in KEEG pathways and gene-disease relations from DisGeNETas mentioned in material and methods. Result of such analysis is described below.

### ***Biological Processes***

More than 4000 biological processes (BPs) are associated with 2834 common deregulated genes; associations of 1019 BPs are significant ( $p \leq 0.05$ ) without correction for multiple testing and 362 BPs are associated significantly (adjusted  $p \leq 0.05$ ). The most significantly (adjusted  $p = 1.42E^{-23}$ ) associated BP was regulation of transcription from RNA polymerase II promoter (GO:0006357). Out of 2834 common genes, 359 genes belong to this BP. Many other transcription/transcription regulations related to BPs was also enriched. We grouped significantly associated BPs related to (i) viral life cycle and growth (133 unique genes), (ii) cytokines (357 genes), (iii) immunity (124 genes), (iv) interferon (80 genes), (v) inflammation (50 genes), (vi) autophagy (94 genes), (vii) apoptosis (154 genes), (viii) cell cycle (194 genes), (ix) NF $\kappa$ B signaling (100 genes), (x) ubiquitin mediated processes (246 genes) and (xi) oxidative stress (83 genes) (**Supplementary Table S6B**). Representative result for BPs associated with viral life cycle and growth is shown in **Figure 1**. Altogether, these processes had 866 unique genes; one gene may be associated with more than one biological process. Detailed result and relevant related biological processes are shown in the Supplementary **Tables S6A and S6B**.



**Figure 1 A:** Enriched biological processes related to viral growth and life cycle with common altered expression of genes in SARS-CoV and CKD. Number of genes in biological processes from left to right viral process (GO:0016032, 59), viral gene expression (GO:0019080, 36), negative regulation of viral life cycle (GO:1903901, 24), viral transcription (GO:0019083, 35), regulation of viral genome replication (GO:0045069, 23), viral life cycle (GO:0019058, 29), regulation of defense response to virus by host (GO:0050691, 11), transport of virus (GO:0046794, 17), intracellular transport of virus (GO:0075733, 17), clathrin-dependent endocytosis (GO:0072583, 13), negative regulation of defense response to virus (GO:0050687, 6), positive regulation of viral life cycle (GO:1903902, 14) and regulation of endocytosis (GO:0030100, 19). Total numbers of gene coded by the human genome in each GO term were 220, 110, 61, 113, 63, 107, 30, 54, 54, 39, 11, 44 and 69 respectively.

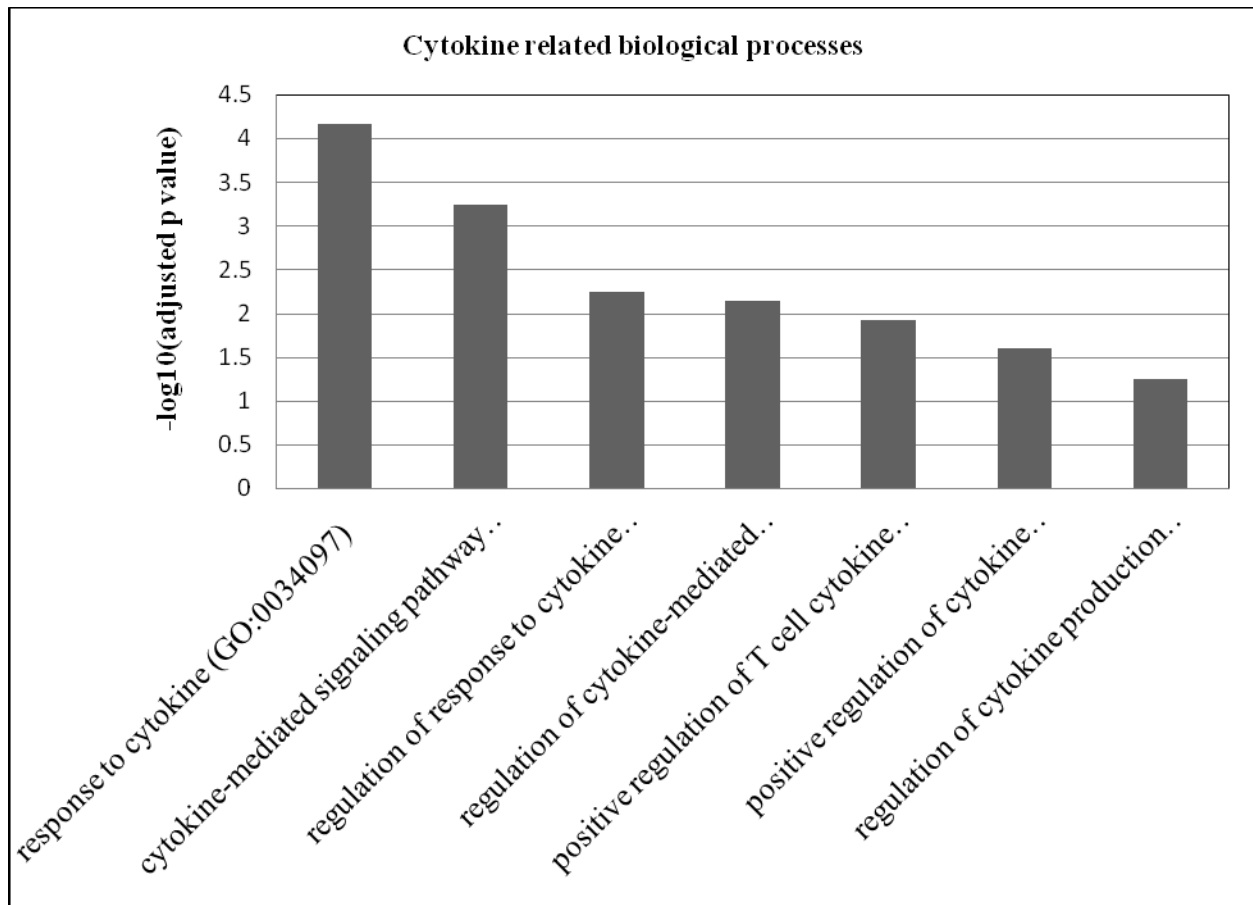


Figure 1B: Representative result of enriched biological processes related to cytokines with common deregulated genes in SARS-CoV and CKD. From left to right response to cytokine (GO:0034097, 42 genes), cytokine-mediated signaling pathway (GO:0019221, 129 genes), regulation of response to cytokine stimulus (GO:0060759, 10 genes), regulation of cytokine-mediated signaling pathway (GO:0001959, 26 genes), positive regulation of T cell cytokine production (GO:0002726, 7 genes), positive regulation of cytokine production (GO:0001819, 48 genes) and regulation of cytokine production (GO:0001817, 26 genes); total number of genes in these processes are 138, 633, 20, 90, 11, 220 and 108 respectively.

#### Enriched KEGG pathways

Enrichment analysis revealed that 301 KEGG pathways are associated with common deregulated genes in SARS-CoV infected cells and CKD (Supplementary **Table S7A**); enrichment of 87 pathways was statistically significant (adjusted  $p \leq 0.05$ ). We again grouped these significantly enriched pathways related to (i) viral and bacterial infections, (ii) immunity and inflammation,

(iii) cell cycle, apoptosis and autophagy, (iv) proteasome and ubiquitin mediated proteolysis and (v) signaling. Detail result is shown in the Supplementary **Table S7B**.

Enrichment of pathways related to viral and bacterial infection with the genes deregulated in SARS-CoV infection and also common to CKD indicates that there might be similarity in alteration of functions of the genes in host response to different infections and renal dysfunctions in CKD. Viral hepatitis infections have been identified among kidney disease patients and have strong impact on the clinical course of kidney disease [63-65]. Infectious disease contributes to excess morbidity with end-stage kidney disease and is considered to be an important complication in patients with end-stage renal disease. Evidence from epidemiological studies has revealed that in mild to moderate stages of CKD increases risk for infection. Altered immune response, compromised T cells, B cells and neutrophil functions, impairing immune functions, increased oxidative stress, inflammation and others in CKD patients could be underlying mechanisms for such increased risk of infection. Vaccination against influenza and pneumococcal for high-risk CKD patients have been proposed to avoid infection (reviewed in Ishigami and Matsushita [66]).

#### *Enrichment of terms in DisGeNET with common deregulated genes in SARS-CoV and CKD*

DisGeNET contains publicly available collections of genes associated with disease and/or traits associated with disease. Gene-disease/trait relations are collected from expert-curated repositories, catalogues of Genome-Wide Association Studies, animal models and the published literature [67]. This data was accessed through <https://amp.pharm.mssm.edu/Enrichr/> [43, 44]. Enrichment analysis revealed that 544 disease/trait was significantly (adjusted  $p \leq 0.05$ ) associated with common deregulated genes in SARS-CoV and CKD. We have grouped the associated diseases (except cancers) related to (i) infectious diseases, (ii) kidney, (iii) heart, (iv) lung, (v) liver, (vi) autoimmune diseases and (vii) anemia. Altogether, these diseases/traits are associated with 1180 deregulated genes; one gene may be associated with more than one disease/trait conditions.

Infectious diseases associated with commonly deregulated genes in our study are Hepatitis C, Hepatitis B, Influenza, HIV infections, enterovirus infections, primary infection NOS, cytomegalovirus infections, dengue fever, chronic hepatitis, Leishmaniasis, pneumocystis jiroveci pneumonia, measles retroviridae infections, respiratory syncytial virus infections and

acquired immunodeficiency syndrome. Host genes associated with these infectious diseases as well as deregulated in SARS-infection indicates that these genes might be involved in infection as well as in CKD.

Defective renal functions in CKD increases the risk of CVD, mortality in CVD is 2-3 fold higher in patients with advanced stage of CKD [68]. CKD is relevant comorbidity in COPD patients; 7.1% of COPD patients have been diagnosed with CKD. CKD is a predictor for mortality independently from other cardiovascular comorbidities [69]. NAFLD might be a risk factor for the development and progression of CKD, sharing cardio-metabolic risk factors and possible common pathophysiological mechanisms [70]. Infection with hepatitis B and C results in chronic liver diseases and can lead to glomerular disease. Interconnection between chronic liver disease and CKD during after hepatitis B and C infections might be mediated through circulating immune complexes or complexes formed in situ [71]. SARS-CoV was observed in different tissues including lung, renal tubule, liver, pancreas and others but absent in heart [72]. Altered expression of genes in SARS-CoV infected cells used in this study could reflect the changed expression of genes in infected organs. Pathological changes in these organs might be caused directly by either the cytopathic effect through replication of SARS-CoV in respective organs or indirectly through systemic responses to respiratory failure or immune response induced by viral infection. Even though CVD and liver disease in COVID-19 patients are risk for severity and mortality, it is not known whether SARS-CoV-2 infect directly to heart or liver [5].

Patients with autoimmune disease like rheumatoid arthritis (RA) are at a higher risk of infection with SARS-CoV-2 due to their immune-compromised state resulting from their underlying immune conditions. Immune-modulatory therapies such as biologics could be used for COVID-19. As of April 1, 2020, among COVID-19 patients originated from Europe, North America, South America, Asia, Africa, and Oceania, only 110 individuals with rheumatic disease have been identified [73]. In this study, 19 (17%) of 110 patients was identified with rheumatic disease [73]. So far no convincing evidences are available for the relationship of arthritis and osteoporosis with COVID-19. However, in a meta-analysis, significantly increased risk of incident CKD among patients with RA compared with individuals without RA was observed [74]. Increased circulating inflammatory cytokines representing as chronic inflammatory condition among aged individuals contributes to development of osteoporosis, CVD and CKD. In patients with renal insufficiency, observed of bone and mineral disorders may accelerate aging

and is a risk factor for cardiovascular death in these patients. Changes in mineral and bone metabolism in the early stages of CKD might accelerate aging, osteoporosis and CVD [75]. Thus association of common genes deregulated in CKD and SARS-CoV with arthritis and osteoporosis related disorders might represent relationship between CKD and these diseases. It remains to be found out whether arthritis and osteoporosis are also observed among COVID-19 patients.

A COVID-19 male patient of age 80 years with multiple comorbidities including severe anemia was reported. Treatment with antiviral drug and recombinant erythropoietin for 7 days improved drastically the conditions. Erythropoietin modulates cytokines and exerts cytoprotective and anti-apoptotic effects. Besides, erythropoietin removes intracellular iron, requires for viral enzymatic activity. This may provide an unfavorable condition for the growth of the virus [76]. This result shows that anemia may complicate the outcome of COVID-19. Eleven COVID-19 patients with Thalassaemic patients did not show and additional severity [77]. CKD associated with anemia has poor outcome. Anemia in CKD results from a complex processes due to shortened erythrocyte survival, erythropoietin deficiency, defective iron homeostasis and uremic-induced inhibitors [78].

### **Deregulated genes coded for viral proteins by SARS-CoV and SARS-CoV-2 interacts with proteins coded by host genes and deregulated in CKD**

Out of 2834 common genes deregulated in SARS-CoV infected cells in vitro and CKD, 1659 genes were associated with relevant BPs, KEGG pathways and disease terms for infections, kidney dysfunctions and other possible comorbid conditions like heart disease, diabetes, liver disease and others. Comparing the unique 569 host proteins that interact with proteins coded by SARS-CoV-2 and SARS-CoV (**Supplementary Table S4B**), we observed that 74 common deregulated genes in SARS-CoV infected cells and CKD also interact with viral proteins.

### **Discussion**

Common genes are deregulated in same direction in SARS-CoV infected cells and CKD. Various biological processes and pathways enriched with the common deregulated genes are relevant for infectious diseases in general as well as CKD. Deregulated genes are significantly associated with several diseases, especially related to lung, kidney, liver and heart. We further

observed that 1591 deregulated genes are common between SARS-CoV infected cells and AKI, enriched biological processes enriched with these genes were also similar to that obtained with CKD and SARS-CoV infection (**data not shown**). Severity of COVID-19 patients with renal abnormality could be due the common genes deregulated in viral infection and renal conditions like CKD and or AKI.

Various biological processes and pathways enriched with the common deregulated genes like apoptosis, autophagy, cell cycle, cytokine, interferon, immune function, inflammation related BPs, signaling pathways like NF-kappa B signaling, p53 signaling, insulin resistance, insulin signaling, FoxO signaling, VEGF signaling, AGE-RAGE signaling, IL-17 signaling, ubiquitin mediated proteolysis, mTOR signaling, relaxin signaling pathways have been implicated in CKD, AKI and various conditions of infections (for detail please see the **Supplementary Text**). Role of infection in clinical course of kidney disease including excess morbidity in end-stage kidney disease has been observed and reviewed [63-66]. Role of cytokines in immune response and inflammation in kidney damage including AKI and CKD is well documented and has been reviewed [79]. Expression of 13 interleukin and interleukin receptors (IL11, IL17RA, IL17RC, IL18, IL1A, IL1F10, IL1R1, IL1RAP, IL1RL2, IL20RB, IL34, IL6 and ILF3) is increased in CKD and SARS-CoV infected cells (**Supplementary Table S5A**). It was revealed from our analysis that these genes are associated with not only with kidney disease like diabetic nephropathy (IL18, IL1A and IL6), ischemia of kidney (IL11, IL18, IL1A and IL6) and renal fibrosis (IL18, IL6) but also in different other diseases/conditions like autoimmune diseases, heart diseases and liver diseases. Interleukins were also associated with many infectious diseases like acquired immunodeficiency syndrome (IL18, IL1A and IL6), Dengue fever (IL11, IL18, IL6 and ILF3), Hepatitis B (IL18, IL1A, IL34 and IL6), Hepatitis C (IL18, IL1A, IL6 and ILF3), Herpes Simplex virus (IL11, IL18 and IL6), HIV (IL18, IL1A, IL6 and ILF3) and others. Biological processes and pathways associated with genes coding or interleukin and interleukin receptors include AGE-RAGE signaling pathway in diabetic complications (IL1A and IL6), apoptotic process (IL1A), cellular response to interleukin-1 (IL1A, IL1R1, IL1RAP and IL6), cytokine-mediated signaling pathway (IL11, IL17RA, IL17RC, IL18, IL1A, IL1F10, IL1R1, IL1RAP, IL1RL2, IL20RB, IL34 and IL6), inflammatory response (IL18, IL1A and IL6), negative regulation of viral life cycle (ILF3), neutrophil mediated immunity (IL6), NF-kappa B signaling pathway (IL1R1), positive regulation of I-kappaB kinase/NF-kappaB signaling (IL1A),



positive regulation of cell cycle process (IL1A), positive regulation of cytokine production (IL17RA, IL18, IL1A and IL6), positive regulation of T cell cytokine production (IL6). Expression of pro-inflammatory cytokine TNF was increased in SARS-CoV infected cells as well as in CKD (**Supplementary Table S5A**). TNF is associated with diabetic nephropathy, heart related disease, liver disease including NAFLD together with many infectious diseases like Dengue Fever, chronic Hepatitis, Leishmaniasis, Measles, Retroviridae Infections, Respiratory Syncytial Virus Infections, Acquired Immunodeficiency Syndrome, Enterovirus Infections and others. Excess production of early response proinflammatory cytokines like TNF, IL6 results in a cytokine storm and results in increased risk of vascular hyperpermeability, multiorgan failure, and eventually death when the high cytokine concentrations are increased over time in acute respiratory distress syndrome (ARDS) [40]. Cytokine storm has also been observed in COVID-19 [80]. Thus, increased levels of interleukins and interleukin receptors in the SARS-Cov infected cells and in CDK alter many processes and pathways relevant or kidney damage by modulating cytokines and thus inflammation and immunity observed in our analysis might be true for COVID-19. Our result further shows that alterations of expressions of genes modify many biological processes and pathways relevant for kidney damage as well as infection of SARS-CoV. Alteration of gene expression may thus contribute to the comorbidity of kidney dysfunction observed in COVID-19.

Mechanism(s) of deregulation of genes in viral infected cells is not fully understood. There are many possibilities like hijacking the transcription factors/regulators due to interactions of viral proteins with host proteins. Interaction of host with SARS-CoV coded proteins PLpro, ORF 3b, ORF 6, N proteins, ORF8 interferes with transcription ability of interferon regulatory factor 3 (IRF3) and reviewed [81]. Other mechanisms include altered epigenetic changes like DNA methylation, histone modifications, altered expression of microRNAs, negative regulator of protein-coding genes and recently discovered long non-coding RNA that can regulate gene expression at transcription and post transcription levels. Possible role of epigenetic changes in SARS-CoV and MERS-COV has been reviewed [82]. MERS-CoV infection alters DNA methylation modifying the expression of genes associated with antigen presentation [83]. Altered expression of several microRNA in acute respiratory infections including human coronavirus has been reported and reviewed [84, 85]. Several long non-coding RNA was identified in viral-infected lungs from mouse. Subsets of long non-coding RNAs are likely to play important role in

respiratory virus pathogenesis [86]. It remains to be found out whether similar mechanism (s) of gene regulation is operative in SARS-CoV-2 infection in COVID-19.

### Conclusion

Molecular connection between COVID-19 and kidney disease/traits including AKI and CKD could be due to altered gene expression observed in SARS-infected cells and CKD. Patients with pre-existing renal abnormality like CKD when infected with SARS-CoV-2, pre-existing altered biological functions, localized or systemic, which are also deregulated due to infection would additively or synergistically altered. This might enhance the growth, survival and pathogenicity of the virus (Figure 2). This might be true for AKI. It remains to be found out whether CKD patients when infected with SARS-CoV-2 results in progression of CKD to ESRD. However, viral infection in COVID-19 might induce AKI [17]. It remains unknown whether AKI induced by viral infection would in long term induce CKD or not as has been observed for SARS-CoV infection to induce diabetes [87]. CKD has been prone to pneumonia [88]. However, evidences are lacking to show that CKD is susceptible to infection with SARS-CoV-2. Understanding the molecular relationship may not only help in management and treatment of kidney damage among COVID-19 patients but also help in treatment of COVID-19 patients.

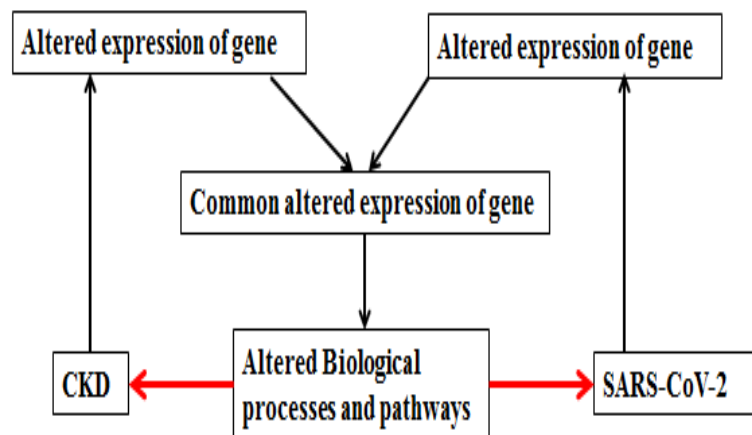


Figure 2: Possible mechanism of abnormal kidney conditions (elevated creatinine, proteinuria, hematuria, AKI, CKD) in COVID-19 patients. Altered expression of genes has been identified in PBMC and kidney of CKD patients and SARS-CoV-2 infected cells. Based on many similarities in genomic organization, proteins structures and pathogens between SARS-CoV-2 and SARS-CoV,

we assumed that similar altered gene expression would also be observed in SARS-CoV-2 infected cells. Common deregulated genes were significantly enriched with many biological processes and pathways, independently relevant for infection as well as in CKD. These altered biological functions may contribute to severity and mortality of COVID-19.

### **Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### **Disclosure of potential conflicts of interest**

The authors declare no conflict of interest.

### **References**

- [1] Y. Yi, P.N.P. Lagniton, S. Ye, et al., COVID-19: what has been learned and to be learned about the novel coronavirus disease, *Int J Biol Sci*, 16 (2020) 1753-1766, doi: 10.7150/ijbs.45134.
- [2] T. Novel Coronavirus Pneumonia Emergency Response Epidemiology, [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China], *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi*, 41 (2020) 145-151, doi: 10.3760/cma.j.issn.0254-6450.2020.02.003.
- [3] F. Zhou, T. Yu, R. Du, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, *The Lancet*, 395 (2020) 1054-1062, doi: 10.1016/s0140-6736(20)30566-3.
- [4] M. Yuan, W. Yin, Z. Tao, et al., Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China, *PloS one*, 15 (2020) e0230548, doi: 10.1371/journal.pone.0230548.
- [5] J. Yang, Y. Zheng, X. Gou, et al., Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis, *Int J Infect Dis*, 94 (2020) 91-95, doi: 10.1016/j.ijid.2020.03.017.

- [6] N. Chen, M. Zhou, X. Dong, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, *The Lancet*, 395 (2020) 507-513, doi: 10.1016/s0140-6736(20)30211-7.
- [7] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *The Lancet*, 395 (2020) 497-506, doi: 10.1016/s0140-6736(20)30183-5.
- [8] W.-j. Guan, Z.-y. Ni, Y. Hu, et al., Clinical Characteristics of Coronavirus Disease 2019 in China, *New England Journal of Medicine*, 382 (2020) 1708-1720, doi: 10.1056/NEJMoa2002032.
- [9] Y.M. Arabi, A.A. Arifi, H.H. Balkhy, et al., Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection, *Annals of internal medicine*, 160 (2014) 389-397, doi: 10.7326/m13-2486.
- [10] J. Gu, E. Gong, B. Zhang, et al., Multiple organ infection and the pathogenesis of SARS, *J Exp Med*, 202 (2005) 415-424, doi: 10.1084/jem.20050828.
- [11] Y. Cheng, R. Luo, K. Wang, et al., Kidney disease is associated with in-hospital death of patients with COVID-19, *Kidney international*, 97 (2020) 829–838, doi: <https://doi.org/10.1016/j.kint.2020.03.005>.
- [12] T. Chen, D. Wu, H. Chen, et al., Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study, *BMJ*, 368 (2020) m1091, doi: 10.1136/bmj.m1091.
- [13] X. Yang, Y. Yu, J. Xu, et al., Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, *The Lancet Respiratory Medicine*, 8 (2020) 475-481, doi: 10.1016/S2213-2600(20)30079-5.
- [14] M. Arentz, E. Yim, L. Klaff, et al., Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State, *Jama*, 323 (2020) 1612-1614, doi: 10.1001/jama.2020.4326.
- [15] Q. Shi, K. Zhao, J. Yu, et al., Clinical characteristics of 101 COVID-19 nonsurvivors in Wuhan, China: a retrospective study, *medRxiv*, (2020), doi: 10.1101/2020.03.04.20031039.
- [16] B.M. Henry, G. Lippi, Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection, *International urology and nephrology*, 52 (2020) 1193–1194, doi: 10.1007/s11255-020-02451-9.

- [17] V. Fanelli, M. Fiorentino, V. Cantaluppi, et al., Acute kidney injury in SARS-CoV-2 infected patients, *Critical Care*, 24 (2020) 1-3, doi: 10.1186/s13054-020-02872-z.
- [18] Y. Cheng, R. Luo, K. Wang, et al., Kidney impairment is associated with in-hospital death of COVID-19 patients, *medRxiv*, (2020), doi: 10.1101/2020.02.18.20023242.
- [19] J.S. Hirsch, J.H. Ng, D.W. Ross, et al., Acute kidney injury in patients hospitalized with COVID-19, *Kidney International*, 98 (2020) 209-218, doi: 10.1016/j.kint.2020.05.006.
- [20] S. Richardson, J.S. Hirsch, M. Narasimhan, et al., Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area, *JAMA*, 323 (2020) 2052-2059, doi: 10.1001/jama.2020.6775.
- [21] M. Nikpouraghdam, A.J. Farahani, G. Alishiri, et al., Epidemiological Characteristics of Coronavirus Disease 2019 (COVID-19) Patients in IRAN: A single Center Study, *J Clin Virol*, (2020) 104378, doi: 10.1016/j.jcv.2020.104378.
- [22] T. Chen, Z. Dai, P. Mo, et al., Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study, *The Journals of Gerontology*, (2020), doi: 10.1093/gerona/glaa089.
- [23] G. Pei, Z. Zhang, J. Peng, et al., Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia, *Journal of the American Society of Nephrology*, 31 (2020) 1157-1165, doi: 10.1681/ASN.2020030276.
- [24] M. Nikpouraghdam, A. Jalali Farahani, G. Alishiri, et al., Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study, *J Clin Virol*, 127 (2020) 104378, doi: 10.1016/j.jcv.2020.104378.
- [25] Z. Li, M. Wu, J. Yao, et al., Caution on kidney dysfunctions of COVID-19 patients, *SSRN*, (2020), doi: 10.1101/2020.02.08.20021212.
- [26] S. Shi, M. Qin, B. Shen, et al., Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China, *JAMA Cardiology*, (2020) E1-E8, doi: 10.1001/jamacardio.2020.0950.
- [27] L. Wang, X. Li, H. Chen, 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) 2020.2002.2019.20025288, doi: 10.1101/2020.02.19.20025288.

- [28] H. Su, M. Yang, C. Wan, et al., Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China, *Kidney International*, (2020) 1-9, doi: 10.1016/j.kint.2020.04.003.
- [29] C.P. Larsen, T.D. Bourne, J.D. Wilson, et al., Collapsing glomerulopathy in a patient with coronavirus disease 2019 (COVID-19), *Kidney international reports*, 5 (2020) 935–939, doi: 10.1016/j.ekir.2020.04.002.
- [30] C. Ronco, T. Reis, Kidney involvement in COVID-19 and rationale for extracorporeal therapies, *Nature Reviews Nephrology*, 16 (2020) 308–310, doi: 10.1038/s41581-020-0284-7.
- [31] A. Panitchote, O. Mehkri, A. Hasting, et al., Factors associated with acute kidney injury in acute respiratory distress syndrome, *Annals of intensive care*, 9 (2019) 74, doi: 10.1186/s13613-019-0552-5.
- [32] J.A. Jefferson, P.J. Nelson, B. Najafian, et al., Podocyte disorders: core curriculum 2011, *American journal of kidney diseases*, 58 (2011) 666-677, doi: 10.1053/j.ajkd.2011.05.032.
- [33] D. Wichmann, J.-P. Sperhake, M. Lütgehetmann, et al., Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study, *Annals of internal medicine*, (2020), doi: 10.7326/M20-2003.
- [34] L.Y. Belayev, P.M. Palevsky, The link between acute kidney injury and chronic kidney disease, *Curr Opin Nephrol Hypertens*, 23 (2014) 149-154, doi: 10.1097/01.mnh.0000441051.36783.f3.
- [35] A. Zuk, J. Bonventre, Recent advances in acute kidney injury and its consequences and impact on chronic kidney disease, *Curr Opin Nephrol Hypertens*, 28 (2019) 397-405, doi: 10.1097/MNH.0000000000000504.
- [36] L. He, Q. Wei, J. Liu, et al., AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms, *Kidney International*, 92 (2017) 1071-1083, doi: <https://doi.org/10.1016/j.kint.2017.06.030>.
- [37] D. Blanco-Melo, B.E. Nilsson-Payant, W.-C. Liu, et al., SARS-CoV-2 launches a unique transcriptional signature from in vitro, ex vivo, and in vivo systems, *bioRxiv*, (2020), doi: 10.1101/2020.03.24.004655.
- [38] L.F. Ng, M.L. Hibberd, E.-E. Ooi, et al., A human in vitro model system for investigating genome-wide host responses to SARS coronavirus infection, *BMC infectious diseases*, 4 (2004) 34, doi: 10.1186/1471-2334-4-34.

- [39] T. Baas, J.K. Taubenberger, P.Y. Chong, et al., SARS-CoV virus-host interactions and comparative etiologies of acute respiratory distress syndrome as determined by transcriptional and cytokine profiling of formalin-fixed paraffin-embedded tissues, *Journal of interferon & cytokine research*, 26 (2006) 309-317, doi: 10.1089/jir.2006.26.309.
- [40] G.U. Meduri, S. Headley, G. Kohler, et al., Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time, *Chest*, 107 (1995) 1062-1073, doi: 10.1378/chest.107.4.1062.
- [41] M. Bhatia, S. Moochhala, Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome, *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*, 202 (2004) 145-156, doi: 10.1002/path.1491.
- [42] W. Hu, Y.-T. Yen, S. Singh, et al., SARS-CoV regulates immune function-related gene expression in human monocytic cells, *Viral immunology*, 25 (2012) 277-288, doi: 10.1089/vim.2011.0099.
- [43] E.Y. Chen, C.M. Tan, Y. Kou, et al., Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool, *BMC bioinformatics*, 14 (2013) 128, doi: 10.1186/1471-2105-14-128.
- [44] M.V. Kuleshov, M.R. Jones, A.D. Rouillard, et al., Enrichr: a comprehensive gene set enrichment analysis web server 2016 update, *Nucleic acids research*, 44 (2016) W90-W97, doi: 10.1093/nar/gkw377.
- [45] T.S. Fung, D.X. Liu, Human Coronavirus: Host-Pathogen Interaction, *Annual Review of Microbiology*, 73 (2019) 529-557, doi: 10.1146/annurev-micro-020518-115759.
- [46] D.E. Gordon, G.M. Jang, M. Bouhaddou, et al., A SARS-CoV-2 protein interaction map reveals targets for drug repurposing, *Nature*, (2020), doi: 10.1038/s41586-020-2286-9.
- [47] J. Li, M. Guo, X. Tian, et al., Virus-host interactome and proteomic survey of PMBCs from COVID-19 patients reveal potential virulence factors influencing SARS-CoV-2 pathogenesis, *bioRxiv*, (2020), doi: 10.1101/2020.03.31.019216.
- [48] P.H. Guzzi, D. Mercatelli, C. Ceraolo, et al., Master Regulator Analysis of the SARS-CoV-2/Human Interactome, *Journal of Clinical Medicine*, 9 (2020) 982, doi: 10.3390/jcm9040982.
- [49] S. Nakagawa, K. Nishihara, H. Miyata, et al., Molecular markers of tubulointerstitial fibrosis and tubular cell damage in patients with chronic kidney disease, *PloS one*, 10 (2015) e0136994, doi: 10.1371/journal.pone.0136994.

- [50] A. Scherer, O.P. Günther, R.F. Balshaw, et al., Alteration of human blood cell transcriptome in uremia, *BMC medical genomics*, 6 (2013) 23, doi: 10.1186/1755-8794-6-23.
- [51] F. Tajti, C. Kuppe, A. Antoranz, et al., A functional landscape of CKD entities from public transcriptomic data, *Kidney international reports*, 5 (2020) 211-224, doi: 10.1016/j.ekir.2019.11.005.
- [52] K.S. Famulski, D.G. de Freitas, C. Kreepala, et al., Molecular phenotypes of acute kidney injury in kidney transplants, *Journal of the American Society of Nephrology*, 23 (2012) 948-958, doi: 10.1681/ASN.2011090887.
- [53] K. Famulski, J. Reeve, D. De Freitas, et al., Kidney transplants with progressing chronic diseases express high levels of acute kidney injury transcripts, *American Journal of Transplantation*, 13 (2013) 634-644, doi: 10.1111/ajt.12080.
- [54] Y. Liu, L.M. Yan, L. Wan, et al., Viral dynamics in mild and severe cases of COVID-19, *Lancet Infect Dis*, 20 (2020) 656-657, doi: 10.1016/s1473-3099(20)30232-2.
- [55] M. Rossi, S. Delbauve, T. Roumeguère, et al., HO-1 mitigates acute kidney injury and subsequent kidney-lung cross-talk, *Free radical research*, 53 (2019) 1035-1043, doi: 10.1080/10715762.2019.1668936.
- [56] R.K. Basu, D.S. Wheeler, Kidney–lung cross-talk and acute kidney injury, *Pediatric Nephrology*, 28 (2013) 2239-2248, doi: 10.1007/s00467-012-2386-3.
- [57] K. Singbartl, J.V. Bishop, X. Wen, et al., Differential effects of kidney–lung cross-talk during acute kidney injury and bacterial pneumonia, *Kidney international*, 80 (2011) 633-644, doi: 10.1038/ki.2011.201.
- [58] K.H. Chu, W.K. Tsang, C.S. Tang, et al., Acute renal impairment in coronavirus-associated severe acute respiratory syndrome, *Kidney international*, 67 (2005) 698-705, doi: 10.1111/j.1523-1755.2005.67130.x.
- [59] P. Zhou, X.-L. Yang, X.-G. Wang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, *nature*, 579 (2020) 270-273, doi: 10.1038/s41586-020-2012-7.
- [60] S. Srinivasan, H. Cui, Z. Gao, et al., Structural Genomics of SARS-CoV-2 Indicates Evolutionary Conserved Functional Regions of Viral Proteins, *Viruses*, 12 (2020) 360, doi: 10.3390/v12040360.



- [61] M. Cascella, M. Rajnik, A. Cuomo, et al., Features, evaluation and treatment coronavirus (COVID-19), in: Statpearls [internet], StatPearls Publishing, 2020.
- [62] M. Ceccarelli, M. Berretta, E.V. Rullo, et al., Editorial–Differences and similarities between Severe Acute Respiratory Syndrome (SARS)-CoronaVirus (CoV) and SARS-CoV-2. Would a rose by another name smell as sweet?, *European Review for Medical and Pharmacological Sciences*, 24 (2020) 2781-2783, doi: 10.26355/eurrev\_202003\_20551.
- [63] F. Fabrizi, R. Cerutti, E. Ridruejo, Hepatitis B virus infection as a risk factor for chronic kidney disease, *Expert review of clinical pharmacology*, 12 (2019) 867-874, doi: 10.1080/17512433.2019.1657828.
- [64] J.B. Henson, M.E. Sise, The association of hepatitis C infection with the onset of CKD and progression into ESRD, in: *Seminars in dialysis*, vol. 32, Wiley Online Library, 2019, pp. 108-118.
- [65] S. Pol, L. Parlati, M. Jadoul, Hepatitis C virus and the kidney, *Nature Reviews Nephrology*, 15 (2019) 73-86, doi: 10.1038/s41581-018-0081-8.
- [66] J. Ishigami, K. Matsushita, Clinical epidemiology of infectious disease among patients with chronic kidney disease, *Clinical and experimental nephrology*, 23 (2019) 437-447, doi: 10.1007/s10157-018-1641-8.
- [67] J. Piñero, J.M. Ramírez-Anguita, J. Saüch-Pitarch, et al., The DisGeNET knowledge platform for disease genomics: 2019 update, *Nucleic acids research*, 48 (2020) D845-D855, doi: 10.1093/nar/gkz1021.
- [68] S. Said, G.T. Hernandez, The link between chronic kidney disease and cardiovascular disease, *J Nephropathol*, 3 (2014) 99-104, doi: 10.12860/jnp.2014.19.
- [69] F.C. Trudzinski, M. Alqudrah, A. Omlor, et al., Consequences of chronic kidney disease in chronic obstructive pulmonary disease, *Respiratory research*, 20 (2019) 151, doi: 10.1186/s12931-019-1107-x.
- [70] L. Orlić, I. Mikolasevic, Z. Bagic, et al., Chronic kidney disease and nonalcoholic Fatty liver disease-is there a link?, *Gastroenterol Res Pract*, 2014 (2014) 847539-847539, doi: 10.1155/2014/847539.
- [71] C. Gluhovschi, F. Gadalean, A. Kaycsa, et al., Does the antiviral therapy of patients with chronic hepatitis exert nephrotoxic effects?, *Immunopharmacology and immunotoxicology*, 33 (2011) 744-750, doi: 10.3109/08923973.2010.551129.

- [72] Y. Ding, L. He, Q. Zhang, et al., Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways, *The Journal of pathology*, 203 (2004) 622-630, doi: 10.1002/path.1560.
- [73] M.A. Gianfrancesco, K.L. Hyrich, L. Gossec, et al., Rheumatic disease and COVID-19: initial data from the COVID-19 global rheumatology alliance provider registries, *The Lancet Rheumatology*, 2 (2020) E250-E253, doi: 10.1016/S2665-9913(20)30095-3.
- [74] S. Raksasuk, P. Ungprasert, Patients with rheumatoid arthritis have an increased risk of incident chronic kidney disease: a systematic review and meta-analysis of cohort studies, *International Urology and Nephrology*, 52 (2020) 147-154, doi: 10.1007/s11255-019-02346-4.
- [75] S. Mazzaferro, N. De Martini, S. Rotondi, et al., Bone, inflammation and chronic kidney disease, *Clinica chimica acta*, 506 (2020) 236-240, doi: 10.1016/j.cca.2020.03.040.
- [76] A. Hadadi, M. Mortezaazadeh, K. Kolahdouzan, et al., Does recombinant human Erythropoietin administration in critically ill COVID-19 patients have miraculous therapeutic effects?, *Journal of Medical Virology*, 92 (2020) 915–918, doi: 10.1002/jmv.25839.
- [77] I. Motta, M.M. De Amicis, V.M. Pinto, et al., SARS-CoV-2 infection in beta thalassemia: preliminary data from the Italian experience, *American journal of hematology*, (2020), doi: 10.1002/ajh.25840.
- [78] J.L. Babitt, H.Y. Lin, Mechanisms of Anemia in CKD, *Journal of the American Society of Nephrology*, 23 (2012) 1631-1634, doi: 10.1681/asn.2011111078.
- [79] J.J. Carrero, M.I. Yilmaz, B. Lindholm, et al., Cytokine dysregulation in chronic kidney disease: how can we treat it?, *Blood purification*, 26 (2008) 291-299, doi: 10.1159/000126926.
- [80] R.J. Jose, A. Manuel, COVID-19 cytokine storm: the interplay between inflammation and coagulation, *The Lancet. Respiratory medicine*, 8 (2020) e46-e47, doi: 10.1016/S2213-2600(20)30216-2.
- [81] A.H. de Wilde, E.J. Snijder, M. Kikkert, et al., Host factors in coronavirus replication, in: *Roles of Host Gene and Non-coding RNA Expression in Virus Infection*, vol. 419, Springer, 2017, pp. 1-42.
- [82] A. Schäfer, R.S. Baric, Epigenetic landscape during coronavirus infection, *Pathogens*, 6 (2017) 8, doi: 10.3390/pathogens6010008.

- [83] V.D. Menachery, A. Schäfer, K.E. Burnum-Johnson, et al., MERS-CoV and H5N1 influenza virus antagonize antigen presentation by altering the epigenetic landscape, *Proceedings of the National Academy of Sciences*, 115 (2018) E1012-E1021, doi: 10.1073/pnas.1706928115.
- [84] S.A. Leon-Icaza, M. Zeng, A.G. Rosas-Taraco, microRNAs in viral acute respiratory infections: immune regulation, biomarkers, therapy, and vaccines, *ExRNA*, 1 (2019) 1, doi: 10.1186/s41544-018-0004-7.
- [85] M.P. Gantier, A.J. Sadler, B.R. Williams, Fine-tuning of the innate immune response by microRNAs, *Immunology and cell biology*, 85 (2007) 458-462, doi: 10.1038/sj.icb.7100091.
- [86] L. Josset, N. Tchitchek, L.E. Gralinski, et al., Annotation of long non-coding RNAs expressed in collaborative cross founder mice in response to respiratory virus infection reveals a new class of interferon-stimulated transcripts, *RNA biology*, 11 (2014) 875-890, doi: 10.4161/rna.29442.
- [87] J.-K. Yang, S.-S. Lin, X.-J. Ji, et al., Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes, *Acta diabetologica*, 47 (2010) 193-199, doi: 10.1007/s00592-009-0109-4.
- [88] C.-Y. Chou, S.-M. Wang, C.-C. Liang, et al., Risk of pneumonia among patients with chronic kidney disease in outpatient and inpatient settings: a nationwide population-based study, *Medicine*, 93 (2014), doi: 10.1097/MD.0000000000000174.