Analyses of Kidney Biomarkers in Patients With SARS-CoV-2 (COVID-19)

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Abstract- The new coronavirus was first reported in China and caused a widespread global outbreak of pneumonia that spread rapidly across this country and many other countries. Acute kidney injury is one of the important complications of COVID-19, which has been shown in some cases. Exploring the diagnostic features of biomarkers of kidney function in COVID-19 patients may lead to better patient management. We collected laboratory data from 206 people with confirmed COVID-19 disease and evaluated their renal biomarkers, Blood Urea Nitrogen (BUN), and creatinine. The age range of the patients was almost 62 years old. The mean age in the dead patients and recovered patients was 71 and 54 years old, respectively. The average LDH value was 755 U/L, and creatine phosphokinase (CPK) was 267 U/L in the patients. The average BUN was 59.1 U/L, and creatinine was 1.5 U/L in COVID-2019 patients. Among all 193 patients, laboratory results revealed that 163 (85.4 %) patients had an elevated BUN level. Based on creatinine levels for total patients, laboratory results revealed that 49 (25.4 %) patients had an elevated value. The average BUN value in dead patients was 85 mg/dL, while in recovered patients was 40.5 mg/dL (P<0.0001). Also, the average creatinine level in dead patients was 1.86 mg/dL, while in recovered patients was 1.24 mg/dL (P=0.0004). Inflammation following COVID-19 disease causes kidney damage and elevated urea and creatinine levels, which may increase the risk of death in these patients.

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Introduction

Coronavirus disease 2019 (COVID-19) was first identified in Wuhan City, Hubei Province, China, among a cluster of people presenting with pneumonia of unknown cause (1,2). This new coronavirus has led to a global outbreak of severe pneumonia and rapidly spread across China and many other countries (3-7) with so many infections and deaths recorded so far, according to the World Health Organization (http://covid19.who.int). Isolation of the virus from infected humans and its molecular analysis showed that the disease cause was a new coronavirus (CoV) and was initially named 2019-nCoV and later renamed COVID-2019 by the World Health Organization. Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) was the name given to COVID-2019 by the International Committee on Taxonomy of Viruses (ICTV) (8). The WHO has recently announced COVID-19 a major concern of health problems in the world (9). The genomic similarity of SARS- CoV- 2 with MERS- CoV and SARS- CoV is 50% and 79%, respectively, while the similarity with bat coronavirus is 96.3% (10). Studies have shown that SARS-Cov-2 can transmit between humans through direct contact or respiratory droplets (4-8). Adults older than 60 years are the most frequent patients infected with SARS-CoV-2 (11). Among adult patients, the main underlying diseases were cardiovascular events, hypertension, and diabetes mellitus (DM). Fever was the most common symptom. Other symptoms include cough,

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dyspnea, myalgia, headache, and diarrhea (7,11). In severe patients, biomarkers related to infection, inflammatory cytokines, and the count of lymphocytes, leukocytes, and monocytes are changed (12).

Acute kidney injury (AKI) is one of the important complications of COVID-19, which has been shown in some cases (1,7,9). This problem is a strong predictive factor that increases the risk of death (13,14). AKI occurs in 0.5–7% of cases and 2.9–23% of ICU patients (1,7,9). Previous studies have shown that approximately 10% of infected patients develop AKI (13,14). Single-cell RNA sequencing data revealed that renal tubular cells overexpress the Antigen Converting Enzyme 2 (ACE2), indicating that the kidneys are at high risk for coronavirus invasion (15). In people with Acute Respiratory Disease Syndrome (ARDS), age, the severity of the disease, and Diabetes Mellitus (DM) are among the common risk factors for developing AKI (16). Therefore, in patients infected with SARS-CoV-2, determining the risk of AKI is a critical step in the patient's prognosis and prompt implementation of preventive and protective measures (17,18). Here, we evaluated the diagnostic features of biomarkers of kidney function in COVID-19 patients, which may lead to better patient management.

Materials and Methods

Study population

In this retrospective, single-center study, we extracted data regarding 206 patients with confirmed COVID-19 from 15 March to 11 April 2020 at Imam Reza Hospital, Tabriz, Iran. This hospital has been dedicated to COVID-19 patients since the virus outbreak. Thus, patients with COVID-19 have been admitted to all wards of this hospital. COVID-19 infection was confirmed by RT-PCR and chest CT-scan in all hospitalized patients. These patients were analyzed for epidemiological, clinical features, and laboratory data. Pneumonia was diagnosed based on the Infectious Disease Society of the America/American Thoracic Society (IDSA/ATS) guidelines (19). The most prominent clinical symptoms of the patient with pneumonia are fever, cough, pleuritic chest pain, and dyspnea. Throat-swab specimens were collected from all suspicious for COVID-19 at admission and sent for RT-PCR testing. These patients had no history of kidney disease and AKI, and their kidney disease was due to COVID-19 disease. AKI was recognized and classified based on serum creatinine (Cr) or blood urea nitrogen (BUN) levels according to established classification systems (16).

Data collection

We have retrospectively extracted laboratory findings from the hospital information system (HIS) and patients' medical records. The data of kidney function biomarkers, which included BUN and Cr, serum biochemical tests, and complete blood count (CBC) on the admitted day was defined as the day of onset of the disease.

Statistical analysis

We used Excel 2016 software to analyze the data. All quantitative analyses were represented by the mean and standard deviation (STDEV). Furthermore, Spearman correlation coefficients were applied to describe the strength and direction analysis of the linear relationship between BUN, Cr, CPK, Ph, Mg, CK-MB, and LDH variables. Significance was set as a $P<0.05$.

Results

A total of 206 patients with COVID-19 were involved in this study. 89 (43.2 %) patients were recruited from the intensive care unit (ICU), and 117 (56.8 %) patients were recruited from infectious units 1 and 2. Of these 206 patients, 84 (40.8 %) patients included the deceased, and 122 (59.2 %) recovered. Among patients recruited from ICU, 66 (74.1 %) were deceased and 23 (25.8 %) patients recovered. Among patients recruited from infectious wards, 18 (15.3 %) patients deceased and 99 (84.6 %) recovered (Table 1).

The average ages of the patients were 62 years old. They include 126 (61.1%) males and 80 (38.8%) females. The average LDH level was 755 U/L, and creatine phosphokinase (CPK) was 267 U/L. The average AST (SGOT) was 85.4 U/L, ALT (SGPT) was 61.9 U/L, and ALP was 196 U/L. The average BUN was 59.1 U/L, and Cr was 1.5 U/L. White blood cells, platelets, and red blood cell values, and their indexes were normal. Moreover, patients' lymphocyte values decreased. In dead patients, the average of patients was almost 71 years old, 61 (72.6%) patients were male, and 23 (27.4%) were female. In recovered patients, the average age of patients was 54 years old, 65 (53.3%) patients were male, and 57 (46.7%) were female. The average LDH value in dead patients was 1012 U/L, while in recovered patients was 548 U/L ($P<0.0001$). The average CPK value in dead patients was 353 U/L, while in recovered patients was 205 U/L ($P=0.0059$). The average AST in dead patients was 155.0 U/L, while in recovered patients was 37.3 U/L ($P=0.0014$), and the average ALT in dead patients was 110.0 U/L, while in recovered patients was 28.9 U/L ($P=0.0012$), as well as the average ALP in dead patients,

was 212, while in recovered patients was 175 (*P*=0.0311). Most importantly, the average BUN value in dead patients was 85 mg/dL, while in recovered patients was 40.5 mg/dL (*P*<0.0001), as well as the average Cr in dead patients was 1.86 mg/dL, while in recovered patients was 1.24 mg/dL (*P*=0.0004). The results are represented in Table 2.

In total, for 193 patients, the results revealed that 163 (85.4 %) patients had an elevated BUN value. In dead patients (n=82), 79 (96.3 %) patients had an elevated BUN, while in recovered patients (n=111), 84 (75.7 %) patients had an elevated BUN (*P*=0.001). Based on Cr, for total patients, the results revealed that 49 (25.4 %) patients had increased values. In dead patients, 38 (46.3 %) had an elevated Cr, while in recovered patients, 98 (88.3 %) patients have normal Cr (*P*=0.0001) (Table 3).

The BUN and Cr level values have a positive correlation in dead patients (*P*<0.0001). Also, in these patients, there was a positive correlation between BUN and phosphorous and magnesium (*P*<0.0001), as well as, there was a positive correlation between BUN and LDH (*P*=0.087) and CK-MB (*P*=0.001) levels; (Figure 1).

Furthermore, in dead patients, there were strong and direct correlations between BUN and Cr. As well, there was a positive correlation between BUN with AST (SGOT) and ALT (SGPT); (Figure 2). The CBC results indicated that the average lymphocyte percentage in dead patients was significantly decreased compared to recovered patients (*P*<0.0001).

Table 1. Frequency of dead and recovered patients based on hospital units

Demographic information			Total	Death	Recovered
Hospital units	Infectious unit 1	Count	56	7	49
		Percentage	27.2 %	8.3 %	40.1 %
	Infectious unit 2	Count	61	11	50
		Percentage	29.6 %	13.1 %	41 %
	Intensive care unit (ICU)	Count	89	66	23
		Percentage	43.2 %	78.6 %	18.9 %
Total	Count		206	84	122
	percentage		100 %	40.8 %	59.2 %

Table 2. Characteristics and laboratory results of the patients hospitalized with COVID-19 in the Imam Reza Hospital in Tabriz, Iran

Demographic information		No. (%)	Reference ranges	Death n (%)	Recovered n (%)	*P*
Total No		206		84 (41)	122 (59)	
Age, years,		62		70.5	53.5	<0.0001
15-49 yr		57(27.7)		6 (7.1)	51 (41.8)	
50-64 yr		55(26.7)		21 (25)	35 (28.7)	
>65 yr		94(45.6)		57 (67.9)	36 (29.5)	
Sex	**Male**	126 (61)		61 (72.6)	65 (53.3)	0.008
	Female	80 (39)		23 (27.4)	57 (46.7)	
Laboratory measures, Mean (STDEV)						
White blood cell count (10^9/µL)		8.13 (± 5.31)	3·5–9·5	10.4 (± 6.72)	6.53 (± 3.21)	<0.0001
RBC (10^6/µL)		4.48 (± 0.711)	Male: 4.5-6 Female: 3.7-5.5	4.52 (± 0.739)	4.44 (± 0.694)	0.4741
HB (g/L)		13.3 (± 2.17)	Male: 13.5-17.5 Female: 12-15.5	13.5 (± 2.1)	13.2 (± 2.22)	0.3412
HCT (%)		40.1 (± 5.89)	Male: 45-52 Female: 37-48	40.8 (± 5.95)	39.5 (± 5.86)	0.1175
M.C. V (fl/cell)		89.8 (± 6.57)	76-96	91.8 (± 6.9)	89.2 (± 6.21)	0.0743
M.C.H (pg/cell)		29.8 (± 2.92)	25-34	30.0 (± 3.08)	29.8 (± 2.69)	0.6293
M.C.H.C (g/dL)		33.2 (± 2)	31-37	33.1 (± 2.27)	33.4 (± 1.7)	0.3394
Platelet (10^4/µL)		182 (± 95.9)	150-450	176 (± 81.8)	186 (± 106)	0.4915
Lymphocyte (%)		16.8 (± 12.7)	16-45	10.8 (± 9.09)	21.0 (± 13.1)	<0.0001
RDW (%)		13.9 (± 1.5)	11.5-14.5	14.2 (± 1.38)	14.0 (± 3.39)	0.6624
PDW (%)		13.7 (± 2.52)	10-17.9	14.1 (± 2.67)	13.3 (± 2.34)	0.0461
MPV (fl)		10.2 (± 1.06)	9.4-12.3	10.3 (± 1)	10.1 (± 1.09)	0.1961
P_LCR (fl)		27.7 (± 7.76)	7.5-10.5	28.5 (± 7.22)	27.1 (± 8.06)	0.2285
ESR (mm/hr)		42.8 (± 30.3)	<17	44.9 (± 30.1)	41.9 (± 31.1)	0.5796
INR		1.26 (± 0.763)	0.8-1.2	1.32 (± 0.48)	1.23 (± 0.932)	0.4178
PT (s)		15.7 (± 5.34)	11.5-13	17.0 (± 5.82)	14.8 (± 4.89)	0.0077

Cont. table 1

PT-Activity	83.8 (± 16.8)		77.9 (± 18.1)	88.3 (± 14.6)	<0.0001
PTT (s)	37.7 (± 13)	30-45	37.9 (± 8.55)	37.8 (± 15.5)	0.9576
BS (mg/dL)	142 (± 67.9)	75-115	156 (± 75)	131 (± 60.5)	0.0261
BUN (mg/dL)	59.1 (± 44.8)	3.5-23	85 (± 49.8)	40.5 (± 28.6)	<0.0001
Creatinine (mg/dL)	1.5 (± 1.21)	0.5-1.5	1.86 (± 1.34)	1.24 (± 1.04)	0.0004
AST (U/L)	85.4 (± 238)	5.0-31.0	155.0 (± 361)	37.3 (± 20.2)	0.0014
ALT (U/L)	61.9 (± 161)	5.0-47.0	110.0 (± 243)	28.9 (± 18.2)	0.0012
ALP (U/L)	196 (± 125)	64-306	212 (± 145)	175 (± 69.2)	0.0311
Bilirubin-Total (mg/dL)	1.05 (± 0.935)	0.3-1.0	1.26 (± 1.14)	0.80 (± 0.55)	0.0507
Bilirubin-Direct (mg/dL)	0.46 (± 0.883)	0.1-0.3	0.54 (± 0.466)	0.36 (± 0.226)	0.0623
Bilirubin-Indirect (mg/dL)	0.58 (± 0.57)	0.2-0.8	0.69 (± 687)	0.45 (± 0.36)	0.0966
LDH (U/L)	755 (± 585)	140-280	1012 (± 782)	548 (± 178)	<0.0001
CPK (U/L)	267 (± 316)	24-195	353 (± 313)	205 (± 306)	0.0059
CK_MB (U/L)	39.6 (± 76.1)	<24	43.0 (± 34.6)	37.7 (± 92)	0.7803
Albumin (g/dL)	9.13 (± 47.5)	3.6-5.1	3.11 (± 0.451)	16.7 (± 71.3)	0.2439
Calcium-Total (mg/dL)	8.52 (± 0.759)	8.8-10.5	8.11 (± 606)	8.85 (± 0.655)	<0.0001
Phosphorus (mg/dL)	3.43 (± 2.08)	3-4.5	3.97 (± 2.76)	2.91 (± 777)	0.0022
Calcium-ion	1.04 (± 0.0774)	1.0-1.3	1.04 (± 0.0761)	1.04 (± 0.0791)	0.8464
Magnesium (mg/dL)	2.1 (± 0.33)	1.3-2.1	2.23 (± 0.359)	1.98 (± 0.237)	<0.0001

Abbreviations: PDW= platelet distribution width, MPV= mean platelet volume, P_LCR= platelet larger cell ratio, ESR= erythrocyte sedimentation rate, INR= international normalised ratio, PT= prothrombin time, PTT= partial thromboplastin time, BS= blood sugar, BUN= blood urea nitrogen, AST= aspartate aminotransferase, ALT= alanine transaminase, LDH= lactate dehydrogenase, CPK= creatine phosphokinase, CK_MB= creatine kinase_MB

Table 3. Frequency of patients based on normal and elevated BUN and Creatinine values

Demographic information			**Total**	**Death**	**Recovered**
BUN	**Patient with normal value Range: 3.5-23 mg/dL**	Count	30	3	27
		percentage	15.5 %	3.7 %	24.3 %
	Patients with elevated value	Count	163	79	84
		percentage	84.5 %	96.3 %	75.7 %
Total	**Count**		193	82	111
	Percentage		100 %	100 %	100 %
Creatinine	**Patient with normal value Range: 0.5-1.5 mg/dL**	Count	144	44	98
		percentage	74.6 %	53.7 %	88.3 %
	Patients with elevated value	Count	49	38	11
		percentage	25.4 %	46.3 %	9.9 %
Total	**Count**		193	82	111
	percentage		100 %	100 %	100 %

Abbreviations: BUN= blood urea nitrogen

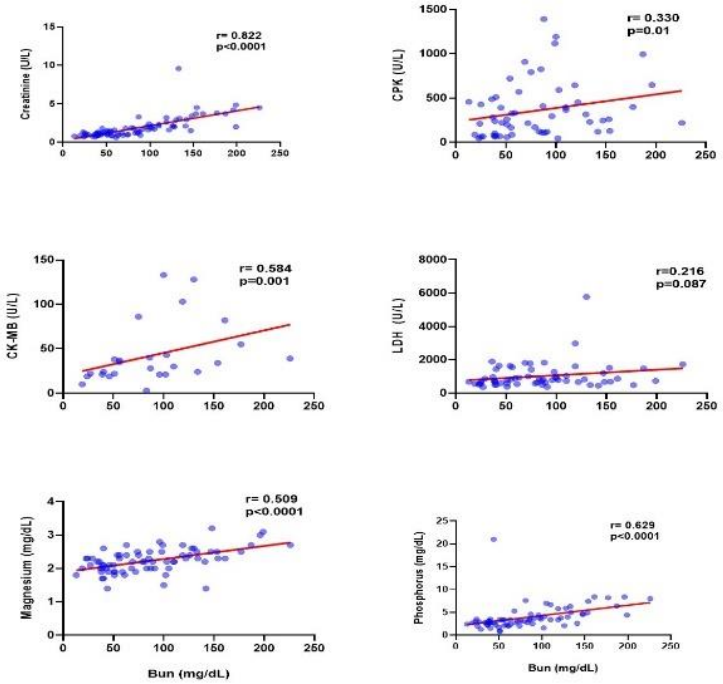

Figure 1. Correlations of BUN with Cr, LDH, CPK, CK-MB, Ph, Mg in dead patients

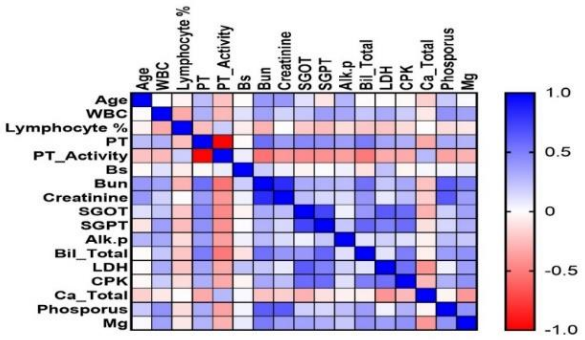

Figure 2. Heatmap of the correlation matrix in dead patients.

Discussion

One of the most important pathogens of the respiratory system is the human coronavirus. SARS-CoV and MERS-CoV are two pathogens that cause a severe respiratory syndrome in humans. The main SARS-CoV outbreak, which affected 8,422 people and spread to 29 countries, happened in 2003 (20). In 2012, MERS-CoV appeared in Middle East countries and then entered China (21). Various elements such as virulence factors of pathogens and the host's immune status affect severe mixed infections. Increased mortality is probably related to factors, such as obesity, aging, and the coexistence of two diseases (22). COVID-19 infection often causes pulmonary involvement, but it can also simultaneously cause damage to other organs such as the heart muscle, kidneys ,and liver (5,23). Here, the effects of SARS-CoV-2 infection on renal function were investigated by analyzing laboratory data from 206 hospitalized COVID-19-confirmed patients. We observed an increment in the factor of kidney injury in these patients. Two important markers for evaluating kidney damage in patients are BUN and Cr. A recent study showed that among patients with SARS-CoV-2, 63% (32/51) had proteinuria, 19% (11/59) had increased Cr, and 27% (16/59) had high urea nitrogen (24).

AKI occurs following a sudden loss of renal operation (25). The main method used to diagnose AKI is an acute change in serum Cr, and the frequency of serum Cr tests have a significant effect on the diagnosis of AKI (26). Therefore, frequent serum Cr analyses should be conducted to improve the early diagnosis of renal impairment in COVID-19 patients. Kidney damage in patients with COVID-19 probably occurs for several reasons. The first reason is the direct destructive effect of the virus on kidney cells. This is confirmed by the identification of coronavirus PCR components in the blood and urine of patients with SARS 2003 (27) and COVID-19 (1). Zhou *et al*., showed that the new coronavirus, like the SARS-CoV, reported in 2003, uses a similar receptor called ACE2 to enter the cells (3). Li *et al*., (24) revealed that some epithelial cells in the intestinal, renal, alveolar, heart, arterial, and gastrointestinal systems have a high expression of ACE2. According to the data obtained from human tissue RNA-sequencing, ACE2 is expressed 100 times more in the genitourinary system (kidney) than in the respiratory system (lung) (24). Thus, kidney disease may develop following the entry of the virus via the ACE2-dependent mechanism. The second reason is to stimulate the immune system-specific responses against the virus (antibodies or specific T-lymphocytes) or to form immune complexes following antigen deposition, both of which may cause kidney damage (28). Indirect effects of cytokines or virus-mediated mediators such as hypoxia, shock, and rhabdomyolysis may be the third leading cause of kidney tissue damage (28). Wang *et al*., (7) reported that serum Cr levels increased in 138 patients with COVID-19 admitted to the ICU. Also, Cheng *et al*., (29) suggested that those with COVID 19 who were high in serum Cr were more likely to be admitted to the ICU and undergo mechanical ventilation. The use of drugs such as umifenovir, oseltamivir lopinavir is recommended in patients who are not in severe conditions of this disease. Because SARS-CoV-2 uses ACE2 to enter the cell, the safety and beneficial impacts of renin-angiotensin-aldosterone system inhibitors in COVID-19 patients should be strictly distinguished (30). Virus fragments can also infect other cells through transmission via the respiratory mucosa, trigger a cytokine storm in the body, induce a set of immune responses, and ultimately alter the number of peripheral blood lymphocytes. The results showed that the total lymphocyte count was reduced in most of the patients. This finding shows that 2019-nCoV, like SARS-CoV, has a great effect on lymphocytes, especially T-lymphocytes. Multiple organ

failure occurs in some patients with ARDS and septic shock. Although in this study a large number of patients were evaluated, several limitations such as the death of some patients with COVID-19, lack of information of patients who were discharged from the hospital, and as a result the inability to the assessment of the long-term effects of COVID disease. Other unknown or unknown confounders may play a role, although we have tried to moderate many confounders in this study. Therefore, COVID-19 disease affects the proper function of the kidney and causes dysfunction in this role, but an accurate evaluation of this disorder and its prevalence in patients with COVID-19 requires further research. We hope that the data from this study will help physicians and nurses identify and properly manage kidney damage from COVID-19 disease.

These data indicate that the prevalence of renal dysfunctions was high in COVID-19 patients hospitalized in Tabriz, Iran. Following infection with COVID-19, nonspecific acute inflammation occurs, resulting in renal damage and an abnormal increase in kidney enzymes. Also, activation of general immunity and the cytokine storm that occurs following infection with COVID-19 may be another cause of increased renal enzymes. Physicians and nurses should increase their knowledge of the renal injury, as people who are hospitalized with COVID-19 disease are more likely to develop AKI. Early recognition of kidney damage and efficient intervention may help decrease mortality in patients with COVID-19.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. Pormohammad A, Ghorbani S, Khatami A, Farzi R, Baradaran B, Turner DL, et al. Comparison of confirmed COVID-19 with SARS and MERS cases-Clinical characteristics, laboratory findings, radiographic signs and outcomes: A systematic review and meta-analysis. Rev Med Virol 2020;30:e2112.
3. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.
4. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med 2020;382:1199-207.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
6. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395:470-3.
7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061.
8. Brunetti O, Derakhshani A, Baradaran B, Galvano A, Russo A, Silvestris N. COVID-19 Infection in Cancer Patients: How Can Oncologists Deal With These Patients? Front Oncol 2020;10:734.
9. Guan W, Ni Z, Hu YY, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
10. Paraskevis D, Kostaki EG, Magiorkinis G, Panayiotakopoulos G, Sourvinos G, Tsiodras S. Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. Infect Genet Evol 2020;79:104212.
11. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020;55:105924.
12. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 2020;81:e6-12.
13. Zhang F, Liang Y. Potential risk of the kidney vulnerable to novel coronavirus 2019 infection. Am J Physiol Physiol 2020;318:F1136-7.
14. Naicker S, Yang C-W, Hwang S-J, Liu B-C, Chen J-H, Jha V. The Novel Coronavirus 2019 epidemic and kidneys. Kidney Int 2020;97:824-8.
15. Deng YY, Zheng Y, Cai GY, Chen XM, Hong Q. Single-cell RNA sequencing data suggest a role for angiotensin-converting enzyme 2 in kidney impairment in patients infected with 2019-novel coronavirus. Chin Med J (Engl) 2020;133:1129-31.
16. Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron Clin Pract 2012;120:c179-84.
17. Ronco C, Navalesi P, Vincent JL. Coronavirus epidemic: preparing for extracorporeal organ support in intensive care. Lancet Respir Med 2020;8:240-1.
18. Kellum JA, Prowle JR. Paradigms of acute kidney injury in the intensive care setting. Nat Rev Nephrol 2018;14:217-30.
19. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG,

Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007;44:S27-72.

20. Hu B, Zeng LP, Yang XL, Ge XY, Zhang W, Li B, et al. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. Drosten C, editor. PLOS Pathog 2017;13:e1006698.
21. Azhar EI, El-Kafrawy SA, Farraj SA, Hassan AM, Al-Saeed MS, Hashem AM, et al. Evidence for Camel-to-Human Transmission of MERS Coronavirus. N Engl J Med 2014;370:2499-505.
22. Wang XF, Shi GC, Wan HY, Hang SG, Chen H, Chen W, et al. Clinical features of three avian influenza H7N9 virus-infected patients in Shanghai. Clin Respir J 2014;8:410-6.
23. Hemmat N, Derakhshani A, Bannazadeh Baghi H, Silvestris N, Baradaran B, De Summa S. Neutrophils, Crucial, or Harmful Immune Cells Involved in Coronavirus Infection: A Bioinformatics Study. Front Genet 2020;11;641.
24. Li Z, Wu M, Guo J, Yao J, Liao X, Song S, et al. Caution on kidney dysfunctions of 2019-nCoV patients. MedRxiv 2020.
25. Vanmassenhove J, Kielstein J, Jörres A, Biesen W Van. Management of patients at risk of acute kidney injury. Lancet 2017;389:2139-51.
26. Ge S, Nie S, Liu Z, Chen C, Zha Y, Qian J, et al. Epidemiology and outcomes of acute kidney injury in elderly chinese patients: a subgroup analysis from the EACH study. BMC Nephrol 2016;17:136.
27. Peiris J, Chu C, Cheng V, Chan K, Hung I, Poon L, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767-72.
28. Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int 2005;67:698-705.
29. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney impairment is associated with in-hospital death of COVID-19 patients. MedRxiv 2020.
30. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259-60.