Clinical Kidney Journal, 2021, vol. 14, no. 10, 2151–2157

doi: 10.1093/ckj/sfab107
Advance Access Publication Date: 11 July 2021
CKJ Review

CKJ REVIEW

Acute tubulointerstitial nephritis and COVID-19

Jia H. Ng [1], Mohamad Zaidan[2], Kenar D. Jhaveri[1] and Hassan Izzedine [3,]

[1]Department of Medicine, Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, USA, [2]Department of Nephrology, Dialysis, Transplantation, Bicêtre University Hospital, Paris-Saclay University, AP-HP, DMU CORREVE Maladies du Coeur et Des Vaisseaux, Le Kremlin-Bicêtre, France and [3]Department of Nephrology, Peupliers Private Hospital, Ramsay Générale de Santé, Paris, France

Correspondence to: Hassan Izzedine; E-mail: h.izzedine@ramsaygds.fr

ABSTRACT

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic that to date has spread to >100 countries. Acute kidney injury is not uncommon with this disease. The most common kidney biopsy finding is acute tubular injury. Glomerular diseases such as collapsing glomerulopathy and vasculitis, and thrombotic microangiopathy have been reported. Viral inclusion particles with distinctive spikes in the tubular epithelium and podocytes, and endothelial cells of the glomerular capillary loops, have been visualized by electron microscopy by some but disputed by others as non-viral structures. Interstitial infiltrates have not commonly been described in the published kidney biopsy series from patients with COVID-19. Medications used to treat COVID-19 can lead to interstitial nephritis, but very few have been reported. In summary, interstitial kidney disease is a rare finding in COVID-19.

Keywords: acute tubulointerstitial nephritis, coronavirus, SARS-CoV-2

CASE VIGNETTE

A 59-year-old male with a past medical history of hypertension, coronary artery disease presents with cough and shortness of breath. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is confirmed. In 24 h, he gets intubated for worsening pulmonary function. Within 8 h of intubation, acute kidney injury (AKI) ensues. He is on steroids and tocilizumab. He is started on remdisivir, Vitamin C and pantoprozole as well. Within the next 24 h, he requires kidney replacement therapy.

Coronaviruses (CoVs) are enveloped, single positive-stranded RNA viruses, which belong to the subfamily Coronavirinae. CoVs have long been recognized as causative agents in self-limited upper respiratory tract infections affecting humans [1] and can be divided into low pathogenic and highly pathogenic CoVs [2]. The low pathogenic CoVs account for 10–30% of upper respiratory tract infections and typically cause mild respiratory diseases [3]. In contrast, the highly pathogenic CoVs, known as novel coronavirus (nCoV), including SARS, Middle East respiratory syndrome (MERS) CoV and the more recent 2019-nCoV or SARS-CoV-2 predominantly infect lower airways and cause fatal pneumonia [4]. These three highly pathogenic β-CoVs have posed a substantial threat to public health.

SARS-CoV was first described as a new human infection in Guangdong province, China in 2002 (World Health Organization 2020) and ended in July 2003. It infected 8096 people and caused 774 deaths with an overall mortality rate of about 9.6% [5, 6]. According to the National Health Service, no new cases of SARS-CoV infection have been reported in humans since 2004 [7].

MERS CoV was first identified in Jordan in 2012 (World Health Organization 2019) and has caused a total of 2494 laboratory-confirmed cases and 858 deaths from 27 countries (mortality rate, 34.4%) since September 2012 [8]. In addition,

Received: 12.4.2021; Editorial decision: 14.6.2021

MERS is still considered to be an ongoing epidemic but appears to be limited to its area of origin [8, 9].

SARS-CoV-2/coronavirus disease 2019 (COVID-19) is an ongoing pandemic that to date has spread to >100 countries (World Health Organization 2020). The estimated case fatality rates (CFRs) for COVID-19 are to be around 2.3% [10]. Nonetheless, despite its lower CFR, COVID-19 has now caused orders of magnitude more deaths than SARS and MERS combined [11].

Viral nephropathy may be caused by viruses themselves or virus-induced immune mechanisms. This article summarizes current evidence on tubulointerstitial kidney disease during CoVs infection.

AKI IN CoV INFECTION

Epidemiology

Kidney involvement of human CoV was noticed when the SARS-CoV epidemic occurred in the early 2000s. AKI was reported in 6.7% of 536 patients with SARS-CoV [12] and was an independent risk factor predicting mortality [13] SARS-CoV patients developed AKI at a median duration of 20 days from the onset of viral infection [14]. The detection of polymerase chain reaction fragments of coronavirus in urine from 21% to 50% of SARS patients between the second and the third week of the viral infection implied a possibility of kidney tropism of the CoV [15].

AKI appears to be frequent in the context of MERS. In a Saudi cohort, 30 out of 70 MERS patients (42.9%) developed AKI during the course of their illness [16]. Among critically ill MERS patients, AKI was reported to develop in 75% of them [13, 17]. Progressive impairment of renal function and AKI start 9–12 days after symptom onset among MERS patients, compared with a median of 20 days for SARS patients [12, 17, 18]. However, despite the presence of viral particles in renal proximal tubular epithelial cell, no evidence of concurrent tubulointerstitial nephritis was identified [19].

AKI is a frequent complication of SARS-CoV-2 (Table 1) and is associated with mortality especially when dialysis is required [20–48].

Assessment of data from major published cohorts on COVID-19, combining results from intensive care unit (ICU) admissions with non-ICU admission, reveals an overall AKI incidence of around 4.2% [32, 42, 49–52]. Among the non-survivors, the incidence of AKI is ∼30% and renal replacement therapy (RRT) is required in 19.5%. Comparatively, in the SARS outbreak in 2003, the incidence of AKI was around 6.7% and multivariate analysis showed AKI as a significant independent risk factor for predicting mortality [relative risk: 4.057; 99% confidence interval (CI): 1.461–11.27; $P < 0.001$] [12].

In China, the reported incidence of AKI in hospitalized patients with COVID-19 ranged from 0.5% to 29% [31, 32, 35, 53] and occurred within a median of 7–14 days after admission [31, 53].

Studies from the USA have reported much higher rates of AKI. In a study of nearly 5500 patients admitted with COVID-19 in a New York City hospital system, AKI occurred in 37%, with 14% of the patients requiring dialysis [39]. About one-third were diagnosed with AKI within 24 h of admission in this study. Of note, these rates are much higher than those reported during the SARS-CoV epidemic [12]. AKI occurred at much higher rates in critically ill patients admitted to New York City hospitals, ranging from 78% to 90% [19, 37–39, 54]. Of 257 patients admitted to ICUs in a study from New York City, 31% received RRT [38].

In a multicentre cohort study of 3099 critically ill adults with COVID-19 admitted to ICUs at 67 hospitals across the USA, AKI-RRT is common among critically ill patients with COVID-19 (20.6%) and is associated with a hospital mortality rate of >60%. Among those who survive to discharge, 33.8% still depend on RRT at discharge and 18.1% remain RRT dependent 60 days after ICU admission. Patient-level risk factors for AKI-RRT included chronic kidney disease (CKD), men, non-White race, hypertension, diabetes mellitus, higher body mass index, higher D-dimer and greater severity of hypoxaemia on ICU admission. Predictors of 28-day mortality in patients with AKI-RRT were older age, severe oliguria and admission to a hospital with fewer ICU beds or one with greater regional density of COVID-19 [40].

In an observational retrospective cohort study including 9657 patients admitted with COVID-19 limited to the New York metropolitan area during the peak of the COVID-19 pandemic (between 1 March 2020 and 27 April 2020), AKI in hospitalized patients with COVID-19 was associated with significant risk for death. Among patients with AKI Stages 1–3 who survived, 74.1% achieved kidney recovery by the time of discharge. Among those with AKI receiving dialysis who survived, 30.6% remained on dialysis at discharge, and pre-hospitalization CKD was the only independent risk factor associated with needing dialysis at discharge (adjusted odds ratio: 9.3; 95% CI: 2.3–37.8) [41].

Spectrum of renal pathologic abnormalities during SARS-CoV-2 infection

Case reports and autopsy series have revealed that most patients with COVID-19-associated AKI have evidence of prominent acute tubular necrosis and diffuse erythrocyte aggregation, specific dysfunction of the proximal tubules (loss of the brush border, intratubular debris and reduced expression of the endocytosis receptor megalin in the brush border), endothelial damage and capillary occlusions, tubules and glomerular complement complex deposit [55–59]. More recent findings support SARS-CoV-2 kidney tropism. A higher SARS-CoV-2 viral load in urine sediments from COVID-19 patients correlated with increased incidence of AKI and mortality [60]. A mild associated interstitial infiltrate may be present [60]. Other biopsy findings have included collapsing glomerulopathy associated with African ancestry and a high-risk APOL1 genotype [59, 61, 62], thrombotic microangiopathy and diverse underlying kidney diseases [56, 59, 63–65]. Kidney infarction has also been reported [66] (Table 2).

Viral inclusion particles with distinctive spikes in the tubular epithelium and podocytes, and endothelial cells of the glomerular capillary loops, have been visualized by electron microscopy [57, 58, 67] and may support this possibility, although the clinical significance of this remains unknown [68, 69].

The demonstration of lymphocytic endotheliitis in the kidney, in addition to viral inclusion particles in glomerular capillary endothelial cells, suggests that microvascular dysfunction is secondary to endothelial damage [67]. Other potential etiologies of AKI common to critical illness presentations, including acute respiratory distress syndrome, rhabdomyolysis, volume depletion and interstitial nephritis, all remain relevant in patients with COVID-19 [70].

Acute tubulointerstitial nephritis during SARS-CoV-2 infection

Acute interstitial nephritis (AIN) is not a rare cause of AKI but it remains a Cinderella among other causes, being underrecognized and underdiagnosed despite the fact that it is a serious

Table 1. Incidence data on AKI in COVID-19 patients [20–48]

Ref.	City/country	Patients, *n*	AKI (%)	RRT (%)	Mortality
[23]	Wuhan	116	0	4	NR
[27]	Wuhan	99	3	9; 39 in ICU	NR
[28]	Wuhan	138	4; 8 in ICU	2; 6 in ICU	NR
[29]	Wuhan	333	11; 43 in ICU	3 in ICU	57%
[30]	Wuhan	701	5	NR	34%
[20]	Wuhan	41	7; 23 in ICU	7; 23 in ICU	NR
[31]	Wuhan	274	11	1	NR
[9]	Wuhan	191	15	5	NR
[32]	Wuhan	52	29	17	NR
[33]	Wuhan	102	20	6	NR
[35]	China	1099	0.5; 6 in ICU	0.8; 12 in ICU	NR
[36]	Jiangsu	80	3	1	NR
[21]	New York	5700	24	4	NR
[37]	New York	1000	34; 78 in ICU	14; 35 in ICU	NR
[38]	New York	257	NR	31	NR
[39]	New York	5449	37; 76 in ICU	23 in ICU	35% with AKI died (6% in non-AKI) 55% with RRT died
[43]	New York	3235		43; 68 in ICU	45% with AKI died (7% in non-AKI)
[40]	New York	3099		20.6	63.3%
[41]	New York	9657	39.9	6.6	46.4% in AKI Stages 1–3 group 79.3% in AKI dialysis-dependent group
[42]	Washington	21	19	NR	NR
[44]	Louisiana	575	28; 61 in ICU	15; 73 in ICU	50%; 72% in patients on RRT
[45]	USA	2215	43	20	NR
[46]	UK	10 547	NR	27	57%
[47]	France	71	80	18	7%
[48]	France	100	81	16	35% with AKI (5% in non-AKI)

NR, not reported.

Table 2. COVID-19-associated kidney disease [57, 60, 65, 66, 67]

Acute tubulointerstitial injury
Acute tubule epithelial damage of varying degrees
Acute damage of the proximal tubules
Systemic capillary leak syndrome
Interstitial edema and/or nephritis
Glomerular disease
– Podocytopathy:
Minimal change disease
Collapsing focal segmental hyalinosis in African ancestry patient with high-risk APOL1 genotype
– Endotheliopathy:
TMA
– Others:
Membranous nephropathy, crescentic GN (ANCA vasculitis and anti-GBM), IgA nephropathy and lupus nephritis
Small fibrin thrombi in the glomerular capillaries consistent with disseminated intravascular coagulation
Miscellaneous
Myoglobin cast nephropathy
Oxalate nephropathy
Renal cortical necrosis
Renal infarction
Renal artery stenosis

ANCA, anti polynuclear neutrophil cytoplasmic antibodies; GBM, glomerular basement membrane; GN, glomerulonephritis; TMA, thrombotic microangiopathy.

reversible disease that can cause CKD and end-stage renal disease . The same probably applies to COVID-19.

AIN is a disease of tubular dysfunction with insidious onset that usually starts as non-oliguric acute renal failure with signs of tubulointerstitial damage that are present but rarely dominate, therefore high clinical suspicion is necessary for timely diagnosis at its reversible stage and early treatment that highly impacts its outcome.

AIN, as one of the differential diagnoses of kidney injury in COVID-19 patients, should therefore be important part of the equation when deciding on medications including steroids.

Although AIN remains uncommon during COVID-19 infection (Table 3) [64, 71–74], several mechanisms may explain such findings (Figure 1).

Specific interstitial infiltration. Interstitial infiltrates have not commonly been described in the published kidney biopsy series from patients with COVID-19 [56, 58, 63].

SARS-CoV-2 has been detected in a kidney allograft [71] associated with a mononuclear cell infiltrate, indicating that the virus is able to enter renal parenchyma and may cause interstitial nephritis. Recent post mortem histopathological analyses showed positive immunostaining with SARS-CoV nucleoprotein antibody in tubules, which supports these findings [57].

It is important to pay attention to low molecular weight proteinuria (Pu) and ionic disorders, as they precede AKI and tubulointerstitial involvement [75].

Werion *et al.* [76] established that SARS-CoV-2 causes specific manifestations of proximal tubule dysfunction as attested by low molecular weight Pu (70–80%), neutral aminoaciduria (46%) and defective handling of uric acid (46%) or phosphate (19%), but not of glucose, corresponding to a partial renal Fanconi syndrome. Proximal tubule dysfunction was independent of pre-existing comorbidities, nephrotoxic medications or

Table 3. AIN and COVID-19

Ref.	Study (age, gender)	Presentation	Pathological finding	Outcome related to AIN
[73]	Case report 69 years, M	AKI	Interstitial mononuclear cell infiltrate Mild acute tubular damage No cellular or antibody-mediated rejection Positive RNA SARS-CoV-2 in tubular cells and interstitium	MMF paused Hydrocortisone administered SCr return to baseline level
[74]	Case report 62 years, M	AKI requiring CVVHDF Minimal Pu Microscopic Hu		ICU Methylprednisolone Kidney function improved (43 mL/min) No longer required dialysis
[75]	Case series 47 pts, 80.9% M	AKI	Mononuclear cell infiltration (80% of cases); CD3+T and CD68+ macrophages	NA
[76]	Case series 13 pts, 92.3% M	AKI Nephrotic-range Pu	Diffuse interstitial infiltration in 8/13 cases but no isolated case of AIN	NA
[66]	Case series 17 pts, 47.1% M	AK Nephrotic-range Pu	FSGS, ATI and AIN in 3/17 patients	NA

M, male; pts, patients; ATI, acute tubular injury; FSGS, focal segmental glomerulosclerosis; MMF, mycophenolate mofetil; SCr, serum creatinine; CVVHDF, continuous veno-venous haemodiafiltration; Hu haematuria; NA, not available.

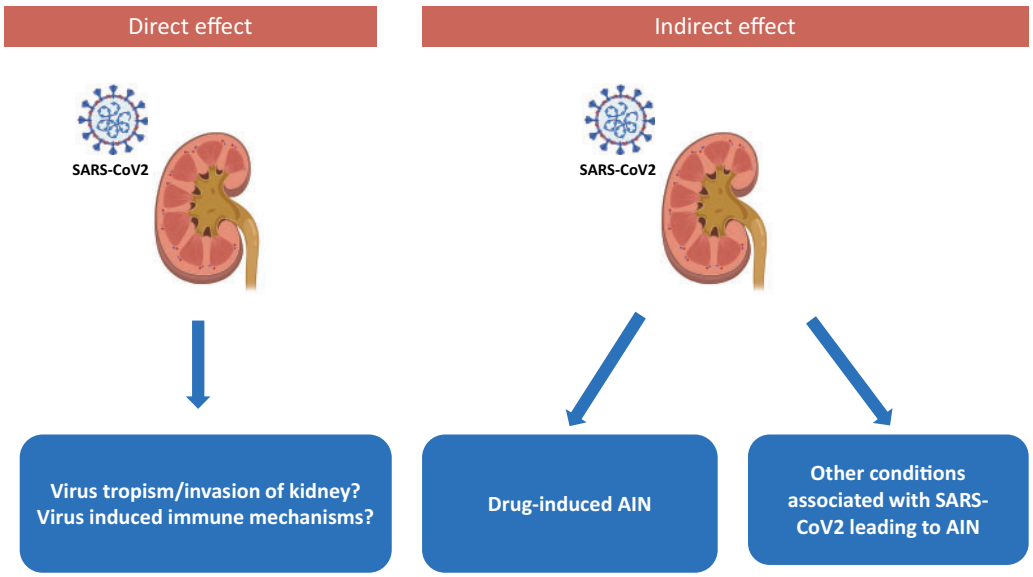

FIGURE 1: AIN during SARS CoV2 infection: mechanisms

viral load. At the structural level, kidneys from patients with COVID-19 showed prominent tubular injury, including in the initial part of the proximal tubule, with brush border loss, acute tubular necrosis, intraluminal debris and a marked decrease in the expression of megalin in the brush border [76]. Among features of proximal tubule dysfunction, hypouricaemia with inappropriate uricosuria was independently associated with disease severity and with a significant increase in the risk of respiratory failure requiring invasive mechanical ventilation. The molecular mechanisms accounting for such specific defects remain unknown [76].

Even though studies argue against SARS-CoV-2 nephropathy [77], we know that there are many cases of AIN caused by infections remote to the kidney (*Legionella*, leptospirosis and streptococcal organisms), and that might also be a case with SARS-CoV-2. Finding virus or its particles within kidney does not necessarily mean direct clinical–pathological connection with AKI, and vice versa.

Drug-induced AIN

Medication-induced nephrotoxicity is a relatively common cause affecting the tubulointerstitial compartment [78, 79]. However, despite patients with severe COVID-19 in the ICU likely receive multiple medications, drug-induced AIN remains uncommon in this setting.

Only case reports of drug reaction with eosinophilia and systemic symptoms syndrome associated with hydroxychloroquine or azithromycin [80] and a drug-induced granulomatous

AIN [72] have been reported in patients with COVID-19, with a good response to corticosteroid therapy.

Furthermore, specific therapeutic treatments for COVID-19 itself such as the use of antiviral agents can potentially induce tubulointerstitial diseases [81–84].

Thus, treatment-related complications need to be considered when determining the etiology of AKI.

Other disease-associated AIN

Several diseases reported to be associated with COVID-19, such as secondary haemophagocytic lymphohistiocytosis [85] and autoimmune haemolytic anaemia [86–88], can induce AIN [88, 89].

CONCLUSION

In summary, even though ATN probably remains the most frequent cause of AKI in clinical settings like COVID-19, and proof of viral replication in human kidney cells remains to be confirmed, one should not forget that it is often hard to differentiate it from AIN that must be one of our differential diagnoses. Besides numerous medications used for COVID-19, AIN in that setting might also be caused not only through direct pathogen invasion of the kidney, but also through different immunologic mechanisms.

CONFLICT OF INTEREST STATEMENT

KDJ serves as a consultant for Astex Pharmaceuticals and Natera and is a paid contributor to Uptodate.com
No disclosure for the other authors.

REFERENCES

1. Falsey AR, McCann RM, Hall WJ *et al.* The "common cold" in frail older persons: impact of rhinovirus and coronavirus in a senior daycare center. *J Am Geriatr Soc* 1997; 45: 706–711
2. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* 2019; 17: 181–192
3. Su S, Wong G, Shi W *et al.* Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol* 2016; 24: 490–502
4. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017; 39: 529–539
5. Drosten C, Günther S, Preiser W *et al.* Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1967–1976
6. Ksiazek TG, Erdman D, Goldsmith CS *et al.*; SARS Working Group. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1953–1966
7. National Health Service. *SARS (Severe Acute Respiratory Syndrome)*. National Health Service, 2019. https://www.nhs.uk/conditions/sars
8. WHO. Middle East Respiratory Syndrome Coronavirus (MERS-CoV). 2020. http://www.who.int/emergencies/mers-cov/en/ (3 March 2021, date last accessed)
9. Al-Tawfiq JA, Kattan RF, Memish ZA. Middle East respiratory syndrome coronavirus disease is rare in children: an update from Saudi Arabia. *World J Clin Pediatr* 2016; 5: 391–396
10. Porcheddu R, Serra C, Kelvin D *et al.* Similarity in case fatality rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. *J Infect Dev Ctries* 2020; 14: 125–128
11. Mahase E. Coronavirus: covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. *BMJ* 2020; 368: m641
12. Chu KH, Tsang WK, Tang CS *et al.* Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int* 2005; 67: 698–705
13. Cha RH, Joh JS, Jeong I *et al.*; Critical Care Team of National Medical Center. Renal complications and their prognosis in Korean patients with Middle East respiratory syndrome-coronavirus from the central MERS-CoV designated hospital. *J Korean Med Sci* 2015; 30: 1807–1814
14. Lai KN, Tsang KW, Seto WH *et al.* Clinical, laboratory, and radiologic manifestation of SARS. *Curr Infect Dis Rep* 2004; 6: 213–219
15. Peiris JS, Chu CM, Cheng VC *et al.* HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; 361: 1767–1772
16. Saad M, Omrani AS, Baig K *et al.* Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *J Glob Infect Dis* 2014; 29: 301–306
17. Eckerle I, Muller MA, Kallies S *et al.* In-vitro renal epithelial cell infection reveals a viral kidney tropism as a potential mechanism for acute renal failure during Middle East Respiratory Syndrome (MERS) Coronavirus infection. *Virol J* 2013; 10: 359
18. Zaki AM, van Boheemen S, Bestebroer TM *et al.* Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; 367: 1814–1820
19. Alsaad KO, Hajeer AH, Al Balwi M *et al.* Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection—clinicopathological and ultrastructural study. *Histopathology* 2018; 72: 516–524
20. Huang C, Wang Y, Li X *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *Lancet* 2020; 395: 497–506
21. Richardson S, Hirsch JS, Narasimhan M *et al.*; The Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020; 323: 2052–2059
22. Wendel Garcia PD, Fumeaux T, Guerci P *et al.* RISC-19-ICU investigators. Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: initial report of the international RISC-19-ICU prospective observational cohort. *EClinicalMedicine* 2020; 25: 100449
23. Pelayo J, Lo KB, Bhargav R *et al.* Clinical characteristics and outcomes of community- and hospital-acquired acute kidney injury with COVID-19 in a US inner city hospital system. *Cardiorenal Med* 2020; 10: 223–231
24. Becher T, Frerichs I. Mortality in COVID-19 is not merely a question of resource availability. *Lancet Respir Med* 2020; 8: 832–833
25. Karagiannidis C, Mostert C, Hentschker C *et al.* Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. *Lancet Respir Med* 2020; 8: 853–862
26. Wang L, Li X, Chen H *et al.* Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116

hospitalized patients from Wuhan, China. *Am J Nephrol* 2020; 51: 343–348
27. Chen N, Zhou M, Dong X *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507–513
28. Wang D, Hu B, Hu C *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus infected pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061–1069
29. Pei G, Zhang Z, Peng J *et al*. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol* 2020; 31: 1157–1165
30. Cheng Y, Luo R, Wang K *et al*. Kidney disease is associated with in hospital death of patients with COVID-19. *Kidney Int* 2020; 97: 829–838
31. Chen T, Wu D, Chen H *et al*. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; 368: m1091
32. Zhou F, Yu T, Du R *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–1062
33. Yang X, Yu Y, Xu J *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475–481
34. Cao J, Tu WJ, Cheng W *et al*. Clinical features and short-term outcomes of 102 patients with corona virus disease 2019 in Wuhan, China. *Clin Infect Dis* 2020; 71: 748–755
35. Guan WJ, Ni ZY, Hu Y *et al*.; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382: 1708–1720
36. Wu J, Liu J, Zhao X *et al*. Clinical characteristics of imported cases of COVID-19 in Jiangsu province: a multicenter descriptive study. *Clin Infect Dis* 2020; 71: 706–712
37. Argenziano MG, Bruce SL, Slater CL *et al*. Characterization and clinical course of 1000 patients with COVID-19 in New York: retrospective case series. *BMJ* 2020; 369: m1996
38. Cummings MJ, Baldwin MR, Abrams D *et al*. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York city: a prospective cohort study. *Lancet* 2020; 395: 1763–1770
39. Hirsch JS, Ng JH, Ross DW *et al*.; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; 98: 209–218
40. Gupta S, Coca SG, Chan L *et al*.; The STOP-COVID Investigators. AKI treated with renal replacement therapy in critically Ill patients with COVID-19. *J Am Soc Nephrol* 2021; 32: 161–176
41. Ng JH, Hirsch JS, Hazzan A *et al*.; Northwell Nephrology COVID-19 Research Consortium. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. *Am J Kidney Dis* 2021; 77: 204–215
42. Arentz M, Yim E, Klaff L *et al*. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020; 323: 1612–1614
43. Chan L, Chaudhary K, Saha A *et al*. Acute kidney injury in hospitalized patients with COVID-19. *J Am Soc Nephrol* 2021; 32: 151–160
44. Mohamed MM, Lukitsch I, Torres-Ortiz AE *et al*. Acute kidney injury associated with coronavirus disease 2019 in urban New Orleans. *Kidney360* 2020; 1: 614–622
45. Gupta S, Hayek SS, Wang W *et al*.; STOP-COVID Investigators. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern Med* 2020; 180: 1436–1412
46. Intensive Care National Audit and Research Centre. ICNARC Report on COVID-19 in Critical Care Case Mix Programme Database, 2020. www.icnarc.org (15 April 2021, date last accessed)
47. Rubin S, Orieux A, Prevel R *et al*. Characterization of acute kidney injury in critically ill patients with severe coronavirus disease 2019. *Clin Kidney J* 2020; 13: 354–361
48. Joseph A, Zafrani L, Mabrouki A *et al*. Acute kidney injury in patients with SARS-CoV-2 infection. *Ann Intensive Care* 2020; 10: 117
49. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. *JAMA* 2020; 323: 1545–1546
50. Luigi Palmieri XA, Bella A, Bellino S *et al*. *Characteristics of COVID-19 Patients Dying in Italy Report Based on Available Data on March 20th, 2020 Epidemiology for Public Health*. Higher Institute of Health, 2020. https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf (3 March 2021, date last accessed)
51. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med* 2020; 8: 738–742
52. Gupta A, Madhavan MV, Sehgal K *et al*. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; 26: 1017–1032
53. Wu C, Chen X, Cai Y *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180: 934–943
54. Petrilli CM, Jones SA, Yang J *et al*. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; 369: m1966 (doi: 10.1136/bmj.m1966)
55. Bradley BT, Maioli H, Johnston R *et al*. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 2020; 396: 320–332
56. Sharma P, Uppal NN, Wanchoo R *et al*.; Northwell Nephrology COVID-19 Research Consortium. COVID-19-associated kidney injury: a case series of kidney biopsy findings. *J Am Soc Nephrol* 2020; 31: 1948–1958
57. Su H, Yang M, Wan C, *et al*. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; 98: 219–227
58. Puelles VG, Lütgehetmann M, Lindenmeyer MT *et al*. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med* 2020; 383: 590–592
59. Sharma P, Ng JH, Bijol V *et al*. Pathology of COVID-19-associated acute kidney injury. *Clin Kidney J* 2021; 14: i30–i39
60. Caceres P, Savickas G, Murray S *et al*. High SARS-CoV-2 viral load in urine sediment correlates with acute kidney injury and poor COVID-19 outcome. *J Am Soc Nephrol* 2021; doi: 10.1681/ASN.2021010059. Online ahead of print
61. Peleg Y, Kudose S, D'Agati V *et al*. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. *Kidney Int Rep* 2020; 5: 940–945
62. Gaillard F, Ismael S, Sannier A *et al*. Tubuloreticular inclusions in COVID-19-related collapsing glomerulopathy. *Kidney Int* 2020; 98: 241

63. Kudose S, Batal I, Santoriello D *et al*. Kidney biopsy findings in patients with COVID-19. *J Am Soc Nephrol* 2020; 31: 1959–1968
64. Akilesh S, Nast CC, Yamashita M *et al*. Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. *Am J Kidney Dis* 2021; 77: 82–93e1
65. Case R, Ramaniuk A, Martin P *et al*. Systemic capillary leak syndrome secondary to coronavirus disease 2019. *Chest* 2020; 158: e267–e268
66. Post A, den Deurwaarder ESG, Bakker SJL *et al*. Kidney infarction in patients with COVID-19. *Am J Kidney Dis* 2020; 76: 431–435
67. Varga Z, Flammer AJ, Steiger P *et al*. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395: 1417–1418
68. Ng JH, Bijol V, Sparks MA *et al*. Pathophysiology and pathology of acute kidney injury in patients with COVID-19. *Adv Chronic Kidney Dis* 2020; 27: 365–376
69. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. *J Am Soc Nephrol* 2020; 31: 1683–1687
70. Peerapornratana S, Manrique-Caballero CL, Gómez H *et al*. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019; 96: 1083–1099
71. Westhoff TH, Seibert FS, Bauer F *et al*. Allograft infiltration and meningoencephalitis by SARS-CoV-2 in a pancreas-kidney transplant recipient. *Am J Transplant* 2020; 20: 3216–3220
72. Szajek K, Kajdi ME, Luyckx VA *et al*. Granulomatous interstitial nephritis in a patient with SARS-CoV-2 infection. *BMC Nephrol* 2021; 22: 19
73. Ferlicot S, Jamme M, Gaillard F *et al*.; AP-HP/Universities/Inserm COVID-19 Research Collaboration. The spectrum of kidney biopsies in hospitalized patients with COVID-19, acute kidney injury, and/or proteinuria. *Nephrol Dial Transplant* 2021; doi: 10.1093/ndt/gfab042
74. Nasr SH, Alexander MP, Cornell LD *et al*. Kidney biopsy findings in patients with COVID-19, kidney injury, and proteinuria. *Am J Kidney Dis* 2021; 77: 465–468
75. Karras A, Livrozet M, Lazareth H *et al*. Proteinuria and clinical outcomes in hospitalized COVID-19 patients: a retrospective single-center study. *Clin J Am Soc Nephrol* 2021; 16: 514–521
76. Werion A, Belkhir L, Perrot M *et al*.; Cliniques universitaires Saint-Luc (CUSL) COVID-19 Research Group. SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule. *Kidney Int* 2020; 98: 1296–1307
77. Rossi GM, Delsante M, Pilato FP *et al*. Kidney biopsy findings in a critically ill COVID-19 patient with dialysis-dependent acute kidney injury: a case against "SARS-CoV-2 nephropathy". *Kidney Int Rep* 2020; 5: 1100–1105
78. Sales GTM, Foresto RD. Drug-induced nephrotoxicity. *Rev Assoc Med Bras (1992)* 2020; 66 (Suppl 1): s82–s90
79. Naughton CA. Drug-induced nephrotoxicity. *Am Fam Physician* 2008; 78: 743–750
80. Herman A, Matthews M, Mairlot M *et al*. Drug reaction with eosinophilia and systemic symptoms syndrome in a patient with COVID-19. *J Eur Acad Dermatol Venereol* 2020; 34: e768–e700
81. Dordal Culla MT, Herrera-Lasso Regás V, Martí-Garrido J *et al*. Treating COVID-19: review of drug hypersensitivity reactions. *J Investig Allergol Clin Immunol* 2020; 30: 385–399
82. Manjaly Thomas ZR, Leuppi-Taegtmeyer A, Jamiolkowski D *et al*. Emerging treatments in COVID-19: adverse drug reactions including drug hypersensitivities. *J Allergy Clin Immunol* 2020; 146: 786–789
83. Izzedine H, Jhaveri KD, Perazella MA. COVID-19 therapeutic options for patients with kidney disease. *Kidney Int* 2020; 97: 1297–1298
84. Mehta P, McAuley DF, Brown M *et al*.; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395: 1033–1034
85. Hindilerden F, Yonal-Hindilerden I, Akar E *et al*. Severe autoimmune hemolytic anemia in COVID-19 infection, safely treated with steroids. *Mediterr J Hematol Infect Dis* 2020; 12: e2020053
86. Lazarian G, Quinquenel A, Bellal M *et al*. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol* 2020; 190: 29–31
87. Lopez C, Kim J, Pandey A *et al*. Simultaneous onset of COVID-19 and autoimmune haemolytic anaemia. *Br J Haematol* 2020; 190: 31–32
88. Cho E, Cha I, Yoon K *et al*. Hemophagocytic syndrome in a patient with acute tubulointerstitial nephritis secondary to hepatitis A virus infection. *J Korean Med Sci* 2010; 25: 1529–1531
89. Demirkaya E, Atay AA, Musabak U *et al*. Ceftriaxone-related hemolysis and acute renal failure. *Pediatr Nephrol* 2006; 21: 733–736