Acute Kidney Injury in Coronavirus Disease 2019 Infected Patients: A Meta-Analytic Study

Nicola Brienza\(^a\)  Filomena Puntillo\(^b\)  Stefano Romagnoli\(^c\)  Luigi Tritapepe\(^d\)

\(^a\)Department of Emergency and Organ Transplantation, University of Bari “Aldo Moro”, Bari, Italy; \(^b\)Department of Interdisciplinary Medicine, University of Bari “Aldo Moro”, Bari, Italy; \(^c\) Department of Anesthesia and Resuscitation, Careggi University Hospital, University of Florence, Florence, Italy; \(^d\)Department of Anesthesia and Intensive Care, San Camillo Forlanini Hospital, Rome, Italy

Keywords
COVID-19 · Acute kidney injury · Continuous renal replacement therapy · Mortality

Abstract

Introduction: In clinical reports on coronavirus disease 2019 (COVID-19), the incidence of acute kidney injury (AKI) is extremely variable, although AKI is described as an independent risk factor for mortality. A meta-analysis was performed to clarify the incidence and the impact of COVID-19-related AKI on mortality. Methods: All trials reporting the incidence of AKI in COVID-19 patients were searched using MEDLINE, the Cochrane Library, and EMBASE databases (last update April 26, 2020). Results: Ten trials with a sample of 5,166 patients were included. AKI occurred in 947 out of 5,166 (18.3%) patients. AKI incidence was higher in severe cases: 62/305 severe patients developed AKI (20%) versus 27/1,268 non-severe patients (2%) (\(p = 0.00001\)). AKI incidence was higher in severe cases: 62/305 severe patients developed AKI (20%) versus 27/1,268 non-severe patients (2%) (\(p = 0.00001\)). AKI occurred in 475 out of 915 (52%) deceased patients versus 183 out of 2,678 (7%) survivors (\(p = 0.00001\)). Continuous renal replacement therapy was significantly more frequent in severe cases and in dead patients. Conclusion: A significant increase in mortality rate was observed in COVID patients who developed AKI, and AKI incidence was also higher in severe cases. Any supportive strategies to protect kidney could represent valuable intervention to reduce mortality in severe COVID-19 patients.
The common clinical presentations of COVID-19 are fever (98%), cough (76%), and myalgia and fatigue (18% each), with accompanying leukopenia (25%) and lymphopenia (63%) [4–6]. Symptoms of upper respiratory infection with rhinorrhea and productive cough are uncommon, except in children. About 16–20% of cases have been classified as severe or critical. Of the 41 patients described by Huang et al. [7], all had pneumonia with abnormalities on computerized tomographic examination of the chest (bilateral lobular and subsegmental areas of consolidation), and 32% required care from the intensive care unit.

Although diffuse alveolar damage and acute respiratory failure are the main features of COVID-19, the involvement of other organs needs to be explored. After lung infection, the virus may enter the blood, accumulate in kidney, and cause damage to resident renal cells. Indeed, COVID-19 RNA was found in the plasma of 15% of patients by real-time polymerase chain reaction [7]. Of note, it is reported that 6.7% of patients with SARS developed acute kidney injury (AKI), and the mortality of those with AKI was 91.7% [8]. Cohort studies suggested a 3–11% incidence of AKI in those with COVID-19 infection [5, 9], although a recent report has shown higher frequency of renal abnormalities [9]. Computed tomography scan of the kidneys showed reduced density, suggestive of inflammation and edema [10]. Recently, AKI was described as an independent risk factor for patient mortality [11]. Therefore, we performed a meta-analysis of published trials to clarify the incidence and the impact of COVID-19-related AKI on mortality.

Methods

Eligibility Criteria

According to PRISMA and MOOSE [12, 13], studies were searched using the following eligibility criteria. Participants were adult (age 18 years or over) hospitalized patients and outpatients with laboratory-confirmed COVID-19. Studies involving pediatric patients were excluded. All trials reporting the incidence of AKI in COVID-19 patients were analyzed. No publication date or publication status restrictions were imposed when selecting studies. Primary outcome measure was mortality.

Information Sources

Different search strategies were performed to retrieve relevant studies by using MEDLINE, the Cochrane Library, and EMBASE databases (last update April 26, 2020). No date restriction was applied. Additional trials were searched in the DARE database and the reference lists of previously published reviews and retrieved articles.

Search

We used the following terms to search for studies: Covid-19, AKI, kidney failure, renal injury.

Study Selection

Two investigators examined at first each title and abstract to identify potentially relevant articles, and therefore the eligibility of the retrieved full-text articles was independently determined by 2 investigators.

Data Collection Process

Data were independently collected by 2 investigators with any discrepancy resolved by reinspection of the original article. To avoid transcription errors, the data were input into statistical software and rechecked by a third investigator.

Data Items

Data abstraction included type and number of patients, AKI rate and definition, mortality and severity of patients (defined as need of ICU and/or definitions provided by authors), and the use of continuous renal replacement therapy (CRRT).

Risk of Bias in Individual Studies

Although observational studies and downgraded randomized trials generally yield a low rating for quality of evidence, there might be unusual circumstances in which authors could “upgrade” such evidence to moderate or even high quality. Moreover, in some instances, observational studies might better reflect actual patient care. Case-control and cohort studies are potentially susceptible to bias, and any limitations of the data should therefore be critically discussed. Bias may be present in findings from nonrandomized trials as well as in poorly designed or conducted randomized trials. For example, numbers of exclusions in nonrandomized trials are frequently unclear, intervention and outcome assessment are often not performed according to standardized protocols, and outcomes may not be blindly assessed. The biases caused by these problems are likely similar to those occurring in randomized trials. The Cochrane collaboration proposed a 16 (or 15)-item scale that consists of 4 headings: “Was there a comparison? How were groups created? Which parts of the study were prospective? On which variables was comparability assessed?” [13]. The items were designed to characterize key features of studies which, on the basis of the experiences of Non-Randomised Studies Methods Group (NRSMG) of the Cochrane Collaboration and “first principles” (rather than evidence), are suspected to define the major study design categories or to be associated with susceptibility to bias. Therefore, we used this scale to evaluate the risk of bias in trials included.

Summary Measures and Planned Method of Analysis

Meta-analytic techniques (analysis software RevMan, version 5.3 Cochrane Collaboration, Oxford, England, UK) were used to combine studies and obtain odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables. A statistical difference between groups was considered to occur if the pooled 95% CI did not include 1 for the OR. An OR >1 indicates a harmful effect. Two-sided p values were calculated. Statistical heterogeneity and inconsistency were assessed by using the Q and I² tests, respectively. When the p value of the Q-test was <0.10 and/or the I² was >40%, heterogeneity and inconsistency were considered significant. Random-effects was used for all analyses.
Results

Study Selection
The search strategy identified 38 articles. Three articles were identified from the reference list of other articles. After initial screening and subsequent selection, a pool of 18 potentially relevant trials was identified. The subsequent eligibility process excluded 8 articles. Overall, 10 articles with a total sample of 5,166 patients [6, 7, 10, 14–20] were considered for analysis (Fig. 1).

Study Characteristics
All studies were published in 2020. Table 1 depicts the characteristic of included studies, AKI definition, num-

Table 1. Clinical trials included in the meta-analysis

| Study           | Country, year | Trial design | Patients, n | AKI definition | AKI Morality | Severe cases | Severity definition | ICU admission |
|-----------------|---------------|--------------|-------------|----------------|--------------|--------------|---------------------|--------------|
| Cao et al. [20] | China, 2020   | Retrospective| 102         | Not stated     | 20           | 17           | 18                  | Respiratory rate >30/min, oxygen saturation ≤93%, or PaO₂/FiO₂ ratio ≤300 mm Hg |
| Cheng et al. [11]| China, 2020   | Retrospective| 274         | AKIN           | 29           | 113          | N/A                 | Respiratory rate >30/min, oxygen saturation ≤93%, or PaO₂/FiO₂ ratio ≤300 mm Hg |
| Deng et al. [15]| China, 2020   | Retrospective| 225         | N/A            | 20           | 109          | N/A                 | Respiratory rate >30/min, oxygen saturation ≤93%, or PaO₂/FiO₂ ratio ≤300 mm Hg |
| Guan et al. [6] | China, 2020   | Retrospective| 1,099       | AKIN           | 6            | 15           | 173                 | American Thoracic Society guidelines for community-acquired pneumonia |
| Huang et al. [7]| China, 2020   | Retrospective| 41          | KIDGO          | 3            | 6            | 13                  | ICU admission |
| Li et al. [10]  | China, 2020   | Retrospective| 153         | KIDGO          | 95           | 32           | 65                  | Respiratory rate >30/min, oxygen saturation ≤93%, or PaO₂/FiO₂ ratio ≤300 mm Hg |
| Richardson et al. [19]| USA, 2020 | Retrospective| 2,500       | KIDGO          | 553          | 523          | 320                 | N/A |
| Wang et al. [16]| China, 2020   | Retrospective| 138         | KIDGO          | 5            | 6            | 36                  | ICU admission for organ dysfunction |
| Wang et al. [17]| China, 2020   | Retrospective| 116         | KIDGO          | 0            | 7            | N/A                 | N/A |
| Wang et al. [18]| China, 2020   | Retrospective| 344         | KIDGO          | 86           | 133          | 344                 | Respiratory rate >30/min, oxygen saturation ≤93%, or PaO₂/FiO₂ ratio ≤300 mm Hg |

AKI, acute kidney injury; KIDGO, Kidney Disease Improving Global Outcomes; PaO₂, arterial oxygen partial pressure; FiO₂, oxygen inspired fraction.
number of patients, severity (e.g., ICU admission), and mortality. All trials were retrospective, but adopted a clear definition of severity of cases and AKI (except 2) (Table 2).

**Table 2. Risk of bias evaluation in nonrandomized trials as proposed by the Cochrane collaboration**

| Study                  | Was there a comparison? | How were groups created? | Which parts of the study were prospective? | On which variables was comparability assessed? |
|------------------------|-------------------------|--------------------------|--------------------------------------------|-----------------------------------------------|
| Cao et al. [20]        | N                       | N                        | N                                          | N                                             |
| Cheng et al. [11]      | N                       | N                        | Outcomes                                  | N                                             |
| Deng et al. [15]       | N                       | N                        | N                                          | N                                             |
| Guan et al. [6]        | N                       | N                        | Outcomes                                  | N                                             |
| Huang et al. [7]       | N                       | N                        | Outcomes                                  | N                                             |
| Li et al. [10]         | N                       | N                        | Outcomes                                  | N                                             |
| Richardson et al. [19] | N                       | N                        | Outcomes                                  | N                                             |
| Wang et al. [16]       | N                       | N                        | Outcomes                                  | N                                             |
| Wang et al. [17]       | N                       | N                        | Outcomes                                  | N                                             |
| Wang et al. [18]       | N                       | N                        | Outcomes                                  | N                                             |

**AKI, Severity of Patients and Mortality**

Considering all trials, AKI occurred in 947 out of 5,166 (18.3%) patients, while CRRT was performed in 111 out of 4,597 (2.4%) COVID-19 patients. Nine out of 10 studies [6, 7, 10, 14–18, 20] derived from oriental experience with a prevalence of AKI of 866 cases out of 2,532 patients (34%), whereas in the only nonoriental study [19] AKI occurred in 81 out of 2,634 patients (3%).

AKI incidence was higher in severe cases: 62/305 severe patients developed AKI (20%) versus 27/1,268 in nonsevere patients (2%) (OR 10.89, 95% CI 5.03–23.6, p = 0.00001, Q statistic p = 0.23, I² = 29%, 5 trials) (Fig. 2). In severe patients, CRRT was performed in 23 out of 305 patients (7.5%) versus 4 out of 1,268 nonsevere patients (0.3%) (OR 14.75, 95% CI 3.4–64.8, p = 0.0004, Q statistic p = 0.18, I² = 36%, 5 trials).

A significant increase in AKI rate was observed in COVID deceased patients: 475/915 patients with AKI died (52%) versus 183/2678 non-AKI patients (7%) (OR = 31.03, 95% CI 13.95–69.02, p = 0.00001, Q statistic p = 0.08, I² = 56%, 5 trials) (Fig. 3). Excluding the largest trial [19], similar results were found (OR 51.87, 95% CI 23.85–112.84, p = 0.00001, Q statistic p = 0.1, I² = 0%, 4 trials), with no statistical heterogeneity and inconsistency. Eighty-one out of 673 dead patients underwent CRRT in comparison with 3 out of 2351 survivors (OR 51.1, 95% CI 5.5–473, p = 0.0005, Q statistic p = 0.14, I² = 54%, 3 trials).

**Discussion**

The result of the present meta-analysis suggests that AKI was found in a significant fraction of severe COVID-19 patients and that the presence of AKI was significantly associated with the death of COVID-19 patients. The etiology of AKI in COVID-19 is thought to be multifactorial, and the mechanism of kidney involvement may include direct cellular injury due to the virus or sepsis leading to cytokine storm syndrome [21]. Angiotensin-converting enzyme 2 (ACE2) is a carboxypeptidase that preferentially removes carboxy-terminal hydrophobic or basic amino acids [22]. After infection,
SARS-CoV-2 entry starts with the binding of the spike glycoprotein expressed on the viral envelope to ACE2 on the alveolar surface [23]. ACE-2 expression has been reported in other organs, such as the gut, kidneys, and heart [24], and the incidence of abdominal symptoms, cardiac dysfunction, and AKI in COVID-19 patients may suggest that the virus could have a tropism for these organs. A very recent autopic study shows that the infection may involve kidney causing formation of hyaline thrombi in small vessels [25]. Pathogen-induced lung injury produce a “cytokine storm” [26] in which strong proinflammatory response spills over into the systemic circulation, causing hypotension, hyper- or hypothermia, leukocytosis or leukopenia, and often thrombocytopenia. The fall in glomerular filtration secondary to hypotension, hypoxia, vasoconstriction, and sepsis plausibly could contribute to the development of acute tubular necrosis. Other causes of AKI in COVID-19 patients with interstitial pneumonia treated with mechanical ventilation can be related to recruitment maneuvers, higher positive end-expiratory pressure (PEEP), and peak and mean airway pressure, despite it is common to use protective ventilation [27], which may contribute to increase venous pressure and foster kidney congestion. Moreover, bidirectional interaction between lung injury and AKI, mediated by several pathophysiologic, molecular, and cellular mechanisms (e.g., upregulation of cytokine production, deranged nitric oxide metabolism, leukocyte trafficking, increased vascular permeability, pulmonary hemorrhage, and pulmonary hypertension), could contribute to the multifaceted kidney and lung interactions and comorbidity [28].

Cox proportional hazard regression confirmed that elevated baseline serum creatinine and blood urea nitrogen, proteinuria, and hematuria were independent risk factors for in-hospital death after adjusting for age, sex, disease severity, comorbidity, and leukocyte count [11]. Our results confirm the link between AKI and mortality in COVID-19. Of note, the incidence of AKI and use of CRRT were significantly higher in sicker and dead patients. This finding is not surprising, since severely sick patients are more prone to develop organ dysfunctions, and kidney failure can initiate and perpetuate heart and lung injury, but once more underlines the potential multifaceted impact of lung-kidney crosstalk. Therefore, monitoring kidney function must be emphasized even in patients with mild respiratory symptoms, and altered kidney function should be given particular attention after admission in clinical practice. Early detection and treatment of renal abnormalities, including adequate hemodynamic support and avoidance of nephrotoxic drugs, and, if possible, blood purification therapies in severely ill patients, particularly when cytokine release actually plays a role in sustaining inflammation and multiorgan involvement, may help to improve the vital prognosis of COVID-19.

Most of medicines currently prescribed to treat COVID-19 (i.e., oseltamivir, lopinavir/ritonavir, ribavirin, and chloroquine phosphate or hydroxychloroquine sulfate) are metabolized in the liver, and some of their metabolites are found in the urine due to renal excretion. Therefore, injury to the liver and kidneys by impairing metabolism and excretion may affect dosing and concentrations of the above drugs, increasing the risk of toxicity [29]. As a result, frequent and careful monitoring of kidney function might

| Study or subgroup | Events | Total | Weight, % | Odds ratio M-H, Random, [95% CI] | Odds ratio M-H, Random, [95% CI] |
|------------------|--------|-------|-----------|---------------------------------|---------------------------------|
| Cheng T          | 28     | 113   | 12.1      | 52.71 [7.05, 394.12]             |                                 |
| Deng             | 20     | 109   | 7.0       | 53.37 [3.18, 894.38]             |                                 |
| Richardson       | 347    | 553   | 49.3      | 18.23 [14.47, 22.98]             |                                 |
| Wang L           | 0      | 7     | Not estimable |                                 |                                 |
| Wang Y           | 80     | 133   | 31.6      | 51.57 [21.33, 124.69]            |                                 |
| Total [95% CI]   | 915    | 2,678 | 100.0     | 31.03 [13.95, 69.02]             |                                 |
| Total events     | 475    | 183   |           |                                 |                                 |

Heterogeneity: $\tau^2 = 0.32; \chi^2 = 6.84, df = 3 (p = 0.08); I^2 = 56$

Test for overall effect: $Z = 8.42 (p < 0.00001)$
help in achieving optimal drug therapeutic concentrations while reducing the risk of adverse drug reaction [29].

Our study has several limitations. Due to the understandable urgency in producing, synthesizing, and disseminating data during the current pandemic, there has been a noticeable increase in fast track publication of studies. All studies were retrospective, and the risk of reporting, selecting, and publication bias was high, even if all except one adopted well-established AKI definition, assuring at least consistent result for this outcome. At this moment, however, these retrospective trials are the only available evidences and we can only infer data from their results.

Moreover, they included a limited number of patients and were not designed to explore the link between AKI, mortality, and severity of patients. We did not know, for example, what are the risk factors more involved in AKI pathogenesis in COVID-19 patients and which pre-existing condition could more contribute to AKI incidence.

Although we could retrieve consistent definition of AKI according to KDIGO in 9 out of 10 studies and results about CRRT utilization, data regarding AKI severity, presumed pathophysiology, and preventive measure are still lacking. Difference in AKI prevalence between oriental and nonoriental studies (although there was only 1 nonoriental study) is another matter of debate.

Conclusions

Our meta-analytic study, within the limits of the studies included, shows that a significant increase in mortality rate was observed in COVID patients who developed AKI and that AKI incidence was also higher in severe cases. Taken together, these results suggest exercising a high degree of attention in monitoring kidney function of COVID-19 patients particularly in critically ill. Any supportive strategies that are potentially protective for kidney functions (hemodynamic monitoring and optimization, avoiding fluid overload and nephrotoxic drugs, and also considering blood purification treatments) could represent valuable intervention in order to reduce mortality in severe COVID-19 patients.

Statement of Ethics

Ethical approval was not required being a meta-analytic study based on already published studies.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

N.B.: conceptualization, data curation, writing, and editing. F.P.: data collection, writing, and review. S.R.: data collection and review. L.T.: data curation and review.

References

1 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.

2 Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:556–74.

3 World Health Organization. Coronavirus disease (COVID-2019) situation reports. [cited 2020 Apr 14]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

4 Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020 Apr;80(4):388–93.

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 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Apr;382:1708–20.

7 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.

8 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.

9 Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol. 2020 Jun;31(6):1157–65.

10 Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on kidney dysfunctions of 2019-CoV patients. SSRN Electron J. 2020. Forthcoming [cited 2020 Mar 2].

11 Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020 May;97(5):829–38.
12 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7): e1000097.

13 Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). The Cochrane collaboration; 2011. Available from: www.cochrane-handbook.org.

14 Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020 Mar 26; 368:m1091.

15 Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J. 2020 Jun 5;133(11):1261–7.

16 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(11):1061–9.

17 Wang L, Li X, Chen H, Yan S, Li D, Li Y, 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(5):343–8.

18 Wang Y, Lu X, Chen H, Chen T, Su N, Huang F, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med. 2020 Jun 1;201(11):1430–4.

19 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with covid-19 in the New York City area. JAMA. 2020 Apr 22;323(20):2052–9.

20 Cao J, Hu X, Cheng W, Yu L, Jun Tu W, Liu Q. Clinical features and short-term outcomes of 18 patients with corona virus disease 2019 in intensive care unit. Intensive Care Med. 2020;46(5):851–3.

21 Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The novel coronavirus 2019 epidemic and kidneys. Kidney Int. 2020 May;97(5):824–8.

22 Ye M, Wysocki J, William J, Soler MJ, Cokic I, BD. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. J Am Soc Nephrol. 2006 Nov;17(11):3067–75.

23 Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses: drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327–47.

24 Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med. 2020 Jun;46(6):1114–6.

25 Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020 Apr 9;98(1):219–27.

26 Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Revi. 2012;76(1):16–32.

27 Panitchote A, Mehkri O, Hastings A, Hanane T, Demirjian S, Torbic H, et al. Factors associated with acute kidney injury in acute respiratory distress syndrome. Am. Intensive Care. 2019;9:74.

28 Syed F, Slutsky A, Ronco C. Lung–kidney cross-talk in the critically ill patient. Am J Respir Crit Care Med. 2016;194:402–14.

29 Rismanbaf A, Zarei S. Liver and kidney injuries in COVID-19 and their effects on drug therapy; a letter to editor. Arch Acad Emerg Med. 2020;8(1):e17.