The systemic review of subgroup analysis on the incidence of acute kidney injury (AKI) in patients with COVID-19

Zhenjian Xu  
Sun Yat-Sen University

Ying Tang  
Sun Yat-Sen University

Qiuyan Huang  
Sun Yat-Sen University

Sha Fu  
Sun Yat-sen University

Xiaomei Li  
Sun Yat-Sen University

Baojuan Lin  
Sun Yat-Sen University

Anping Xu  
Sun Yat-Sen University

Junzhe Chen (chenjzh23@mail.sysu.edu.cn)  
Sun Yat-sen Memorial Hospital of Sun Yat-sen University

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Abstract

Background: Acute kidney injury (AKI) occurs among patients with Coronavirus disease-19 (COVID-19) and has also been proven to be associated with in-hospital mortality. Remdesivir has been authorized for the treatment of COVID-19 patients. We conducted a systematic review to evaluate the incidence of AKI in hospitalized COVID-19 patients. The incidence of AKI in different subgroups was also investigated.

Method: A thorough search was carried out to find relevant studies in PubMed, Web of Science, medRxiv and EMBASE from 1 Jan 2020 until 1 June 2020. All systemic reviews of proportions were performed using the meta package for R project (4.0.1).

Results: A total of 16199 COVID-19 patients were included in our systematic review. The pooled estimated incidence of AKI in all hospitalized COVID-19 patients was 10.0% (95% CI: 7.0-12.0%). The pooled estimated need for continuous renal replacement therapy (CRRT) in COVID-19 patients was 4% (95% CI: 3-6%). According to our subgroup analysis, the incidence of AKI could be associated with the age, disease severity and the ethnicity of the patients. The incidence of AKI in hospitalized COVID-19 patients being treated with remdesivir was 7% (95% CI: 3-13%) in a total of 5 studies.

Conclusion: We found that AKI was not rare in hospitalized COVID-19 patients. The incidence of AKI could be associated with age, disease severity and ethnicity. Remdesivir probably not induced AKI in COVID-19 patients. Our systemic review provides evidence for future studies that AKI might be closely associated with SARS-CoV-2 infection.

Background

Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to more than 60 million infections and over 1 million deaths worldwide [1]. The mortality of COVID-19 is particularly high among older patients with chronic diseases, including hypertension, diabetes, obesity, chronic kidney disease and cardiac disease [2]. In 2003, the incidence of acute kidney injury (AKI) in patients with SARS was reported to be 6.7%, and 91.7% of patients who died were diagnosed with AKI as a complication [3]. Recent studies have suggested that the incidence of AKI during hospitalization in patients with COVID-19 has a wide range and that AKI is associated with a poor prognosis [4-6]. Continuous renal replacement therapy (CRRT) is usually required for critically ill COVID-19 patients, not only for the treatment of AKI but also to effectively eliminate the cytokine cascade [7]. The requirement of CRRT in COVID-19 cases also needs to be summarized.

Given the current ongoing pandemic of COVID-19, there is a need to identify safe and effective treatment options. Remdesivir, a broad-spectrum antiviral agent, has been shown to have antiviral activity against several RNA viruses, including MERS-CoV and Ebola virus disease (EVD) [8, 9]. As remdesivir effectively inhibits SARS-CoV-2 in vitro and in a mouse model [10, 11], it has been authorized for the treatment of COVID-19 patients in some countries, including the United States [12]. The incidence of AKI in COVID-19 patients being treated with remdesivir is still uncertain. Overall, the exact rate and characteristics of AKI associated with COVID-19 patients are not well understood. In this study, we performed a systemic review of the incidence of AKI in hospitalized patients with COVID-19.

Methods

Search Strategy

A systematic literature search was performed using PubMed, Web of Science, medRxiv and EMBASE from 1 Jan 2020 until 1 June 2020 to summarize the data of AKI among patients hospitalized with COVID-19 and being treated with remdesivir. Two authors independently carried out systematic literature searches employing the terms “kidney” OR “renal” OR “acute kidney injury” OR “acute renal failure” AND “COVID-19” OR “SARS-COV-2” to obtain the data on the AKI incidence in patients hospitalized with COVID-19. No language restrictions were applied.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: 1) observational studies that reported the incidence of AKI in all hospitalized patients with COVID-19, and 2) observational studies or randomized, placebo-controlled trial (RCT) studies that reported the incidence of AKI in hospitalized patients with COVID-19 being treated with remdesivir.
Studies that were 1) editorials, review articles or case reports, 2) preprint article, 3) studies with incomplete information about AKI, and 4) studies that did not utilize the 2012 KDIGO criteria to define AKI were excluded.

**Quality assessment**

The methodological quality of the retrospective cross-sectional studies was assessed independently by two reviewers (Chen and Xu) using the method of the Agency for Healthcare Research and Quality (AHRQ) ([http://www.ncbi.nlm.nih.gov/books/NBK35156](http://www.ncbi.nlm.nih.gov/books/NBK35156)). An item would be scored 0 if it was answered NO or UNCLEAR; if it was answered YES, then the item was scored 1. Studies achieving an 8 or above were considered high quality. At the same time, the randomized controlled trials (RCTs) in our study were analysed using Cochrane Collaboration’s tool ([http://handbook-5-1.cochrane.org/](http://handbook-5-1.cochrane.org/)). It can be divided into groups A, B and C. Studies that achieved an “A” were considered high quality.

**Statistical Analysis**

All systemic reviews of proportions were performed using the meta package for R project (4.0.1). The incidence of AKI in COVID-19 patients (proportion variables) was used in our study. The incidences and their 95% CIs are presented as forest plots by the Metaprop function. Statistical heterogeneity between studies was assessed using the \( \hat{\tau} \) statistic. The random-effects model was used if there was heterogeneity between studies (\( \hat{\tau}<50\% \)); otherwise, the fixed-effects model was adopted. Rate consolidation was conducted using five methods (untransformed, log transformation, logit transformation, arcsine transformation, and Freeman-Tukey double arcsine transformation), and the logit transformation that yielded the results with the lowest \( \hat{\tau} \) was selected for inclusion in our study. Sensitivity analysis was performed by one-by-one exclusion. Peter's test was performed for publication bias, and significance was considered if \( P<0.05 \).

**Results**

**Literature Search and Study Characteristics**

A total of 1852 papers were identified according to our search criteria. After the exclusion based on titles and abstracts, two authors independently looked through 204 papers. Of them, 159 publications were unrelated to AKI and therefore excluded from the study. Forty-five papers received a full-article review, and 23 were excluded according to the exclusion criteria. The flow diagram of the selection process is shown in Fig. 1. Finally, 22 studies including 16199 COVID-19 patients met the predefined inclusion criteria and were used to determine the incidence of AKI in COVID-19 patients. 5 of 22 studies including 972 patients were used to determine the incidence of AKI in COVID-19 patients being treated with remdesivir.

Table 1 show the characteristics of the studies in this systemic review. All studies in our systemic review showing the incidence of AKI were retrospective cross-sectional studies, and most of them were of high quality (12/19). The RCTs included in our study were also of high quality.

**Incidence of AKI in COVID-19 patients**

Overall, 16199 COVID-19 patients were included in our systematic review [5, 6, 13-32]. The pooled estimated incidence of AKI in all hospitalized COVID-19 patients was 10% (95% CI: 7%-12%, Figure 2), and significant heterogeneity (\( I^2=97\%, \text{ Chi-square}= 0.26, P<0.0001 \)) was observed. Meanwhile, a total of 12633 COVID-19 patients in 12 studies were included to investigate the CRRT incidence [5, 14-18, 20-25]. 566 patients (15.6%) need CRRT in 3612 AKI COVID-19 patients. The pooled estimated CRRT incidence in COVID-19 patients was 4% (95% CI: 3-6%, Figure 3).

**Incidence of AKI in different subgroup of COVID-19 patients**

Subgroup analysis was performed according to ethnicity, age and disease severity (Supplementary Figure 1-3). The pooled estimated AKI incidences in the Asian subgroup analysis and non-Asian subgroup analysis were 7% (95%CI: 4%-11%) and 15% (95% CI: 11%-20%), respectively (Supplementary Figure 1). At the same time, the incidence of AKI in the subgroup with a median/mean age greater than 60 years was 12% (95% CI: 9%-16%) and 6% (95% CI: 3%-12%) in the subgroup with a median/mean age less than 60 years (Supplementary Figure 2). In the subgroup of hospitalized patients, the incidence of AKI was 8% (95% CI: 6%-11%), but it was...
26% (95% CI: 21%-31%) in the ICU patients (Supplementary Figure 3). There was still significant heterogeneity in most of the subgroups in our subgroup analysis.

**Incidence of AKI in subgroup of COVID-19 patients being treated with remdesivir**

A total of 5 studies, including 972 COVID-19 patients, investigated the incidence of AKI in hospitalized COVID-19 patients being treated with remdesivir [28-32]. The pooled estimated AKI incidence in hospitalized COVID-19 patients being treated with remdesivir was 7% (95% CI: 3%-13%) (Figure 4). In no remdesivir subgroup of COVID-19 patients, the incidence of AKI was 10% (95% CI: 8%-13%).

**Sensitivity analysis and publication bias**

In the sensitivity analysis, we used the one-by-one exclusion method (Supplementary Figures 4 and 5) and found similar results to our main study. Peter’s test was performed to evaluate publication bias (Table 2), and no significant difference was detected in the analysis of the incidence of AKI in COVID-19 patients.

**Discussion**

In this systemic review, the results from 22 retrospective cross-sectional studies including 16199 patients hospitalized with COVID-19 from 1 January 2020 to 1 June 2020 demonstrated that AKI was not rare in COVID-19. The incidence of AKI might be associated with the age, disease severity and ethnicity of the patients in our subgroup study.

COVID-19 infection is primarily a respiratory disease, but other organs, including the kidneys, are often involved. SARS-CoV-2 enters cells via the angiotensin-converting enzyme 2 (ACE2) receptor and is highly homologous to SARS-CoV [33]. High ACE2 expression in proximal tubular epithelial cells may be a potential target for kidney injury [34]. Renal abnormalities, such as proteinuria, haematuria, and AKI, occur in patients with COVID-19 [35]. AKI is characterized by a rapid increase in serum creatinine, a decrease in urine output, or both [36]. The currently widespread AKI definition was developed by the Kidney Disease Improving Global Outcomes (KDIGO) group in 2012 [37]. The most common causes of AKI were septic shock, post major surgery, cardiogenic shock, drug toxicity and hypovolemia [38]. The cause of AKI in COVID-19 is likely to be multifactorial, including a direct attack by SARS-CoV-2 (COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup) or haemodynamic instability, microcirculatory dysfunction, tubular cell injury, renal congestion, microvascular thrombi and endothelial dysfunction [39], which are commonly found in critically ill patients. Pathology from autopsies of patients with COVID-19 with renal failure revealed that the kidneys showed the presence of viral particles within both the tubular epithelium and the podocytes on electron microscopy [40], varying degrees of acute tubular necrosis (ATN), diffuse proximal tubule injury with the loss of the brush border, nonsymmetric vacuolar degeneration, haemosiderin granules and pigmented casts [40, 41].

We found that the incidence of AKI in COVID-19 patients was 10%. A similar AKI incidence in COVID-19 patients (10.8%) was also reported in other studies [34]. The diversity of patients included in our systemic review caused heterogeneity. According to the subgroup analysis, the estimated AKI incidence of patients with an average age greater than 60 years old was 12%, meanwhile, that of patients with an average age less than 60 years old was 6%. Many reports on COVID-19 have highlighted age-related differences in health outcomes, and the mortality of COVID-19 is particularly high among older patients [42, 43]. Age is also an important risk factor for AKI [44]. The pooled estimated AKI incidence in the Asian subgroup was 7%. But in the non-Asian subgroup, it was 15%. Black ancestry is also a risk factor for AKI [45]. In a large cohort study of hospitalized COVID-19 patients, 76.9% of the patients who were hospitalized with COVID-19 and 70.6% of those who died were black, whereas blacks comprised only 31% of the population [46]. There might be a difference between the criteria for hospital admission in Asian and non-Asian COVID-19 patients. A European study showed that 190/1457 (13%) of COVID-19 patients were diagnosed with AKI on arrival [47]. The incidence of AKI in ICU patients with COVID-19 was particularly high, ranging from 8%-62% [14, 17, 22-24, 26, 27]. In our subgroup analysis, we found that the incidence of AKI was 26% in ICU patients. Critically ill patients hospitalized with COVID-19 who stayed in the ICU were more likely to develop AKI [5]. Lin L proved that disease severity was associated with the incidence of AKI in COVID-19 patients [34].

The incidence of CRRT was 4% in COVID-19 patients according to our investigation. CRRT has been practiced in many sepsis patients complicated with AKI [48]. There has been growing evidence suggests that patients with severe COVID-19 infection may have cytokine storm syndrome [49, 50]. CRRT can remove inflammatory factors, thus blocking the cytokine storm syndrome.
and ultimately reducing the damage inflicted on multiple organs [51]. However, the timing of CRRT in severe COVID-19 remains controversial [49]. Additional research is needed to determine whether early CRRT could improve the prognosis of COVID-19 patients with AKI.

The introduction of antiviral drugs is a common cause of drug-induced AKI [52, 53]. As shown in Figure 4, the incidence of AKI in hospitalized COVID-19 patients being treated with remdesivir was 7%. In the clinical studies of remdesivir, AKI was the most frequent adverse event leading to drug discontinuation [29, 31]. Antiviral drugs cause AKI by many mechanisms, including direct renal tubular toxicity, allergic interstitial nephritis (AIN), and crystal nephropathy [54, 55]. However, in animal models, remdesivir treatment was effective against MERS-CoV and did not show any side effects like AKI [56]. According to a recently published multicentre matched cohort study on remdesivir, remdesivir was not significantly associated with an increased incidence of AKI in COVID-19 patients, even with patients who had baseline eCrCl<30 mL/min [57]. Based on our study, we also did not get evidence for remdesivir associated AKI in COVID-19 patients. More RCTs should be studied for cogent evidence in the future.

Limitations

Our systemic review had some limitations. First, most of the studies included were retrospective cross-sectional studies, although most of them (65%) were high quality. Second, the systemic review of proportions was collected from studies with a single group. Compared with a study with two groups, heterogeneity was more common. There was statistically significant heterogeneity in the systemic review of AKI incidence in COVID-19 patients. The diversity of the included studies involving different disease stages or activities, ages, races and sexes might also be associated with heterogeneity. Although we performed a subgroup study, the results still had significant heterogeneity. As a new and unknown infectious disease, our study only summarized the studies that have already been published on this topic. The potential bias of COVID-19 patients reported may not represent all of the patients hospitalized in the pool of total COVID-19 worldwide patients. Third, there were limited original studies (n<10) for the systemic review of the incidence of AKI in hospitalized COVID-19 patients being treated with remdesivir. Finally, since the investigation of COVID-19 is ongoing, additional clinical data is expected to be published.

Conclusion

According to our study, AKI was common in hospitalized COVID-19 patients. The incidence of AKI could be associated with age, disease severity and ethnicity. Remdesivir probably not induced AKI in COVID-19 patients. Our systemic review demonstrated the clinical characteristics of AKI in COVID-19, providing evidence for future studies that AKI might be closely associated with SARS-CoV-2 infection.

Abbreviations

AKI: acute kidney injury
COVID-19: Coronavirus disease-19
CRRT: Continuous renal replacement therapy
ICU: Intensive care unit
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
EVD: Ebola virus disease
RCTs: Randomized controlled trials

Declarations

Ethics approval

This study was approved by the institutional review board of Sun Yat-sen University.
Consent to publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

All of the authors declared no competing interests.

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Author Contributions

Concept and design: AX and JC.

Acquisition, analysis, or interpretation of data: ZX and JC.

Drafting of the manuscript: ZX and YT.

Critical revision of the manuscript: AX and JC.

Statistical analysis: QH, SF, XL and BL.

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References

1. Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/

2. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, 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(10239):1763-70.

3. Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, Fung KS, Tang HL, Yan WW, Chan HW, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005; 67(2):698-705.

4. Batlle D, Soler MJ, Sparks MA, Hiremath S, South AM, Welling PA, Swaminathan S. Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. J Am Soc Nephrol. 2020; 31(7):1380-3.

5. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane
Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020; 98(1):209-18.

Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020; 97(5):829-38.

Forest SJ, Michler RE, Skendelas JP, DeRose JJ, Friedmann P, Parides MK, Forest SK, Chauhan D, Goldstein DJ. De Novo Renal Failure and Clinical Outcomes of Patients With Critical Coronavirus Disease 2019. Crit Care Med. 2020.

Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020; 11(1):222.

Mulangu S, Dodd LE, Davey RT, Jr., Tshian Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019; 381(24):2293-303.

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30(3):269-71.

Sheahan TP, Sims AC, Zhou S, Graham RL, Pruigssers AJ, Agostini ML, Leist SR, Schafer A, Dinnon KH, 3rd, Stevens LJ, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med. 2020; 12(541).

Lim S, DeBruin DA, Leider JP, Sederstrom N, Lynfield R, Baker JV, Kline S, Kesler S, Rizza S, Wu J, et al. Developing an Ethics Framework for Allocating Remdesivir in the COVID-19 Pandemic. Mayo Clin Proc. 2020; 95(9):1946-54.

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382(18):1708-20.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al.
Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497-506.

15. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020; 5(7):802-10.

16. Wang L, Li X, Chen H, Yan S, Li D, Li Y, Gong Z. 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.

17. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; 323(11):1061-9.

18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, 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(10229):1054-62.

19. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, Jian M, Xu H, Prowle J, Hu B, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care. 2020; 24(1):188.

20. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020; 368:m1091.

21. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020; 146(1):110-8.

22. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, 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(5):475-81.

23. Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, Xu J, Wu Y, Huang C, Ouyang Y, et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: a cross-sectional study. Crit
24. Hong KS, Lee KH, Chung JH, Shin KC, Choi EY, Jin HJ, Jang JG, Lee W, Ahn JH. Clinical Features and Outcomes of 98 Patients Hospitalized with SARS-CoV-2 Infection in Daegu, South Korea: A Brief Descriptive Study. Yonsei Med J. 2020; 61(5):431-7.

25. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, the Northwell C-RC, Barnaby DP, Becker LB, Chelico JD, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020; 323(20):2052-9.

26. Ferguson J, Rosser JI, Quintero O, Scott J, Subramanian A, Gumma M, Rogers A, Kappagoda S. Characteristics and Outcomes of Coronavirus Disease Patients under Nonsurge Conditions, Northern California, USA, March-April 2020. Emerg Infect Dis. 2020; 26(8):1679-85.

27. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 2020; 323(16):1612-4.

28. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020; 383(19):1813-26.

29. Antinori S, Cossu MV, Ridolfo AL, Rech R, Bonazzetti C, Pagani G, Gubertini G, Coen M, Magni C, Castelli A, et al. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post-treatment hospitalisation status. Pharmacol Res. 2020; 158:104899.

30. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020; 382(24):2327-36.

31. Wang Y, Zhou F, Zhang D, Zhao J, Du R, Hu Y, Cheng Z, Gao L, Jin Y, Luo G, et al. Evaluation of the efficacy and safety of intravenous remdesivir in adult patients with severe COVID-19: study protocol for a phase 3 randomized, double-blind, placebo-
controlled, multicentre trial. Trials. 2020; 21(1):422.

32. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020; 383(19):1827-37.

33. Raza A, Estepa A, Chan V, Jafar MS. Acute Renal Failure in Critically Ill COVID-19 Patients With a Focus on the Role of Renal Replacement Therapy: A Review of What We Know So Far. Cureus. 2020; 12(6):e8429.

34. Lin L, Wang X, Ren J, Sun Y, Yu R, Li K, Zheng L, Yang J. Risk factors and prognosis for COVID-19-induced acute kidney injury: a meta-analysis. BMJ Open. 2020; 10(11):e042573.

35. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, Ma Z, Huang Y, Liu W, Yao Y, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol. 2020; 31(6):1157-65.

36. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019; 394(10212):1949-64.

37. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012; 120(4):c179-84.

38. Gameiro J, Fonseca JA, Outerelo C, Lopes JA. Acute Kidney Injury: From Diagnosis to Prevention and Treatment Strategies. J Clin Med. 2020; 9(6).

39. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020; 395(10234):1417-8.

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

41. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural Evidence for Direct Renal Infection with SARS-CoV-2. J Am Soc Nephrol. 2020; 31(8):1683-7.

42. Jing QL, Liu MJ, Zhang ZB, Fang LQ, Yuan J, Zhang AR, Dean NE, Luo L, Ma MM, Longini I, et al. Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study. Lancet Infect Dis.
43. Collaborative CO. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet. 2020; 396(10243):27-38.

44. Thongprayoon C, Hansrivijit P, Kovvuru K, Kanduri SR, Torres-Ortiz A, Acharya P, Gonzalez-Suarez ML, Kaewput W, Bathini T, Cheungpasitporn W. Diagnostics, Risk Factors, Treatment and Outcomes of Acute Kidney Injury in a New Paradigm. J Clin Med. 2020; 9(4).

45. Demirjian S. Race, class, and AKI. J Am Soc Nephrol. 2014; 25(8):1615-7.

46. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. N Engl J Med. 2020; 382(26): 2534-43.

47. Portoles J, Marques M, Lopez-Sanchez P, de Valdenebro M, Munez E, Serrano ML, Malo R, Garcia E, Cuervas V. Chronic kidney disease and acute kidney injury in the COVID-19 Spanish outbreak. Nephrol Dial Transplant. 2020; 35(8):1353-61.

48. Cai C, Qiu G, Hong W, Shen Y, Gong X. Clinical effect and safety of continuous renal replacement therapy in the treatment of neonatal sepsis-related acute kidney injury. BMC Nephrol. 2020; 21(1):286.

49. Chen G, Zhou Y, Ma J, Xia P, Qin Y, Li X. Is there a role for blood purification therapies targeting cytokine storm syndrome in critically severe COVID-19 patients? Ren Fail. 2020; 42(1):483-8.

50. Antinori S, Bonazzetti C, Gubertini G, Capetti A, Pagani C, Morena V, Rimoldi S, Galimberti L, Sarzi-Puttini P, Ridolfo AL. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? Autoimmun Rev. 2020; 19(7):102564.

51. Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P. Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. Nephrol Dial Transplant. 1996; 11(2):293-9.

52. Zavras P, Su Y, Fang J, Stern A, Gupta N, Tang Y, Raval A, Giralt S, Perales MA, Jakubowski AA, et al. Impact of Preemptive Therapy for Cytomegalovirus on
Toxicities after Allogeneic Hematopoietic Cell Transplantation in Clinical Practice: A Retrospective Single-Center Cohort Study. Biol Blood Marrow Transplant. 2020; 26(8):1482-91.

53. Maan R, Al Marzooqi SH, Klair JS, Karkada J, Cerocchi O, Kowgier M, Harrell SM, Rhodes KD, Janssen HLA, Feld JJ, et al. The frequency of acute kidney injury in patients with chronic hepatitis C virus infection treated with sofosbuvir-based regimens. Aliment Pharmacol Ther. 2017; 46(1):46-55.

54. Xing W, Gu L, Zhang X, Xu J, Lu H. A metabolic profiling analysis of the nephrotoxicity of acyclovir in rats using ultra performance liquid chromatography/mass spectrometry. Environ Toxicol Pharmacol. 2016; 46:234-40.

55. Izzedine H, Launay-Vacher V, Deray G. Antiviral drug-induced nephrotoxicity. Am J Kidney Dis. 2005; 45(5):804-17.

56. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, van Doremalen N, Leighton I, Yinda CK, Perez-Perez L, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature. 2020; 585(7824):273-6.

57. Ackley TW, Mcmanus D, Topal JE, Cicali B, Shah S. A Valid Warning or Clinical Lore: An Evaluation of Safety Outcomes of Remdesivir in Patients with Impaired Renal Function from a Multicenter Matched Cohort. Anti-microb Agents Chemother. 2020; AAC.02290-20.

Tables

Table 1. Characteristic of the included studies for the incidence of AKI in hospitalized COVID-19 patients
| Study                  | Year | Country         | Design                                      | Sample size | Age (median/mean) | Male (%) | The diagnosis criteria of AKI                                      | Department | Quality score |
|-----------------------|------|-----------------|---------------------------------------------|-------------|------------------|----------|---------------------------------------------------------------|------------|---------------|
| Yichun Cheng⁶         | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 701         | 63               | 52.4%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | Stage 1 (n=13)  
|                       |      |                 |                                             |             |                  |          | Stage 2 (n=9)  
|                       |      |                 |                                             |             |                  |          | Stage 3 (n=14)  
|                       |      |                 |                                             |             |                  |          | Hospitalized Patients                                      |            | AHRQ 8        |
| Woejie Guan¹³         | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 1099        | 47               | 58.1%    | 2012 KDIGO criteria                                      | Hospitalized Patients | AHRQ 8       |
| Chaolin Huang¹⁴       | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 41          | 49               | 73.0%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 3(7%)                                                 | Hospitalized Patients | AHRQ 8       |
| Shaobo Shi¹⁵          | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 416         | 64               | 49.7%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 3(7%)                                                 | Hospitalized Patients | AHRQ 8       |
| Liwen Wang¹⁶          | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 116         | 54               | 57.8%    | 2012 KDIGO criteria                                      | Hospitalized Patients | AHRQ 8       |
| Dawei Wang¹⁷          | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 138         | 56               | 54.3%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 2(1.45%)                                               | Hospitalized Patients | AHRQ 8       |
| Fei Zhou¹⁸            | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 191         | 56               | 62.0%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 2(1.45%)                                               | Hospitalized Patients | AHRQ 8       |
| Dawei Wang¹⁹          | 2020 | China, Wuhan and Huanggang | Retrospective Cross-sectional study | 107         | 51               | 53.3%    | 2012 KDIGO criteria                                      | Hospitalized Patients | AHRQ 7       |
| Tao Chen²⁰            | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 274         | 62.0             | 62.4%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 3(1%)                                                  | Hospitalized Patients | AHRQ 8       |
| Xiaochen Li²¹         | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 548         | 60               | 50.9%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 2(0.4%)                                                | Hospitalized Patients | AHRQ 8       |
| Xiaobo Yang²²         | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 52          | 51.9             | 70%      | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 9(17%)                                                 | ICU Patients     | AHRQ 7       |
| Yuan Yu²³             | 2020 | China, Wuhan    | Retrospective Cross-sectional study         | 226         | 64               | 61.5%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | Stage 1 (n=23)  
|                       |      |                 |                                             |             |                  |          | Stage 2 (n=12)  
|                       |      |                 |                                             |             |                  |          | Stage 3 (n=22)  
|                       |      |                 |                                             |             |                  |          | ICU Patients                                                | AHRQ 7       |
| KyungSoo Hong²⁴       | 2020 | Korea, Daegu    | Retrospective Cross-sectional study         | 98          | 55.4             | 38.8%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 3(3.1%)                                               | Hospitalized Patients | AHRQ 6       |
| Safiya Richardson²⁵   | 2020 | USA, New York   | Retrospective Cross-sectional study         | 5700        | 63               | 60.3%    | 2012 KDIGO criteria  
|                       |      |                 |                                             |             |                  |          | CRRT 3(3.2%)                                               | Hospitalized Patients | AHRQ 8       |
| Jaime S. Hirsch³      | 2020 | USA, New York   | Retrospective Cross-sectional study         | 5449        | 64.0             | 60.9%    | 2012 KDIGO                                                  | Hospitalized Patients | AHRQ 8       |
### Table 2. Results of the systemic review of the incidence of AKI and CRRT in COVID-19 patients

| Study No. | COVID-19 patients No. | Proportion/OR (95%CI) | Study heterogeneity |
|-----------|------------------------|------------------------|---------------------|
|           |                        |                        | Chi-square test | df | I² | Peter’s test (P value) |
| The incidence of AKI in COVID-19 patients | 22 | 16199 | 0.10(0.07-0.12) | 0.26 | 21 | 97% | 0.18 |
| The incidence of CRRT in COVID-19 patients | 12 | 12633 | 0.04(0.03-0.06) | 0.17 | 11 | 84% | 0.24 |