Whether Remdesivir Increases the Risk of Acute Kidney Injury (AKI) in Patients with COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Background: Acute kidney injury (AKI) occurs among patients with COVID-19, it is also proved to be associated with in-hospital mortality. Remdesivir, an RNA polymerase inhibitor, has shown its antiviral activity in vitro and animal models. The adverse effect of Remdesivir especially AKI is the most common cause which lead to drug discontinuation. Whether Remdesivir increases the risk of AKI in patients with COVID-19 is not clear. We conducted a systematic review and meta-analysis to evaluate the incidence rate of AKI in hospitalized COVID-19 patients and whether Remdesivir increases the risk of AKI.

Methods: A thorough search was carried out to find relevant studies in PubMed, medRxiv, and Web of Science from 1 Jan 2020 till 1 June 2020. 15135 COVID-19 patients and 981 COVID-19 patients using Remdesivir were included in our meta-analysis.

Results: The pooled estimated incidence of AKI in all hospitalized COVID-19 patients was 12.0% (95% CI:9.0%-15.0%). According to our subgroup study, the incidence of AKI was associated with the age, disease severity and race of patients. The incidence of AKI in hospitalized COVID-19 patients using Remdesivir was 6% (95% CI: 3%-13%) with a total of 5 studies. Comparing with COVID-19 patients without Remdesivir treatment, Remdesivir treatment do not increase the risk of AKI in COVID-19 patients showing OR 0.80(95%CI: 0.44-1.46, P>0.05).

Conclusions: We found out that AKI was not rare in hospitalized COVID-19 patients. The incidence of AKI was associated with age, disease severity and race. Remdesivir treatment did not increase the risk of AKI in hospitalized COVID-19 patients. Our meta-analysis may provide an evidence for future study that AKI is associated with the natural cause of COVID-19, not the adverse event after the usage of Remdesivir.

Background

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to more than 10 million of infections and over 500 thousand deaths worldwide\(^1\). Mortality of COVID-19 is particularly high among older patients with chronic diseases, including hypertension, diabetes, obesity, chronic kidney disease and cardiac disease\(^2\). Recent studies suggest that the development of acute kidney injury (AKI) during hospitalization in patients with COVID-19 is high and associated with a poor prognosis\(^3,5\). However, the exact rate of AKI associated with patients hospitalized with COVID-19 is not well understood. In this study, we performed a meta-analysis of the incidence rate of AKI in hospitalized patients with COVID-19.

Given the current, ongoing pandemic of COVID-19, there is a need to identify safe and effective treatment options. Remdesivir (GS-5734), a prodrug of adenosine analogues, has been shown to have antiviral activity against several RNA viruses, including MERS-CoV and Ebola virus disease (EVD)\(^6,7\). Remdesivir effectively inhibit SARS-CoV-2 in vitro and in mice model\(^8,9\). In J.H. Beige et al’s report, Remdesivir was superior to placebo in shortening the time to recovery in patients with COVID-19 and evidence of lower respiratory tract infection\(^10\). But according to the clinical experiment, the adverse effect of Remdesivir especially AKI is the most cause lead to drug discontinuation\(^11,12\). Whether Remdesivir increases the risk of AKI in patients with COVID-19 is still uncertain. Here, we further systematically review and meta-analysis the incidence rate of AKI in COVID-19 with the treatment of Remdesivir.

Methods

Search Strategy

A systematic literature search was performed using PubMed, Web of Science, and medRxiv from 1 Jan 2020 till 1 June 2020 to summarize the data of AKI with patients hospitalized with COVID-19 and using Remdesivir for treatment of COVID-19. Two authors independently carried out systematic literature searches employing the terms “acute kidney injury” OR “acute renal failure” AND “COVID-19” OR “SARS-COV-2” for the data of AKI incidence in patients hospitalized with COVID-19, at the same time, we also employing the terms “Remdesivir” AND “COVID-19” OR “SARS-COV-2” for the data of AKI incidence in COVID-19 patients with the treatment of Remdesivir. 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 rate of AKI in all hospitalized patients with COVID-19 and 2) observational studies or randomized, placebo-controlled trial (RCT) studies that reported the incidence rates of AKI in hospitalized patients with COVID-19 using Remdesivir.
Excluded studies that were 1) editorials, review articles or case reports, 2) studies with incomplete information about AKI, and 3) studies did not utilize the 2012 KDIGO criteria to define AKI.

**Quality assessment**

The methodological quality of retrospective cross-sectional studies was assessed independently by two reviewers (Chen and Xu) using the Agency for Healthcare Research and Quality (AHRQ) ([http://www.ncbi.nlm.nih.gov/books/NBK35156](http://www.ncbi.nlm.nih.gov/books/NBK35156)). Studies achieving 8 or above were considered as high quality. At the same time, the randomized controlled trials (RCTs) in our study were analyzed using Cochrane collaboration’s tool ([http://handbook-5-1.cochrane.org/](http://handbook-5-1.cochrane.org/)). It can be divided as group A, B and C. Studies which achieving “A” were considered as high quality.

**Statistical Analysis**

All the meta-analyses were performed using the R project (4.0.1). The proportion of AKI in COVID-19 patients (ratio variables) and odds ratio (OR) of the AKI incidence rate between different groups using Remdesivir or not (dichotomous variables) were used in our study. All results were reported with 95% confidence intervals (CIs). Statistical heterogeneity between studies was assessed using the chi-square test with significance set at $P < 0.10$ and heterogeneity was quantified using the $I^2$ statistic ($I^2 < 50\%$). The random-effect model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was adopted. Sensitivity analysis was performed by one by one exclusion. Begger’s test was performed for publication bias and the significance was considered if $P < 0.05$.

**Results**

**Literature Search and Study Characteristics**

A total of 204 papers were collected according to our searching criteria. Of them, 159 publications were unrelated with AKI and therefore excluded from the study. 45 papers received full-article review, where 22 were excluded according to the exclusion criteria. The flow diagram of the selection process is shown in Fig. 1. Finally, 18 studies including 15135 all hospitalized COVID-19 patients met the predefined inclusion criteria and were used for the incidence of AKI in all hospitalized COVID-19 patients. At the same time, 5 studies including 981 patients were used for the incidence of AKI in COVID-19 patients using Remdesivir for the treatment of COVID-19. Only two RCTs were chosen to compare the incidence of AKI between COVID-19 patients using Remdesivir or not. These two RCTs were of high quality.

Tables 1 and 2 showed the characteristics of the studies in this systemic review. All studies in our meta-analysis showing the incidence of AKI were retrospective cross-sectional studies and most of them with high quality (13/18). And the RCTs included in our study were also with high quality.
| Study           | Year | Country                  | Design                                      | Sample size | Age (median/mean) | Male (%) | The diagnosis criteria of AKI | Department                          | Quality score |
|----------------|------|--------------------------|---------------------------------------------|-------------|-------------------|----------|-----------------------------|-------------------------------------|---------------|
| Yichun Cheng   | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 701         | 63                | 52.4%    | 2012 KDIGO criteria         | Hospitalized Patients (10.4% ICU) | AHRQ 8        |
| Weijie Guan    | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 1099        | 47                | 58.1%    | 2012 KDIGO criteria         | Hospitalized Patients (5% ICU)     | AHRQ 9        |
| Chaolin Huang  | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 41          | 49                | 73.0%    | 2012 KDIGO criteria         | Hospitalized Patients (32% ICU)    | AHRQ 8        |
| Shaobo Shi     | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 416         | 64                | 49.7%    | 2012 KDIGO criteria         | Hospitalized Patients (7.7% IMV)   | AHRQ 9        |
| Luwen Wang     | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 116         | 54                | 57.8%    | 2012 KDIGO criteria         | Hospitalized Patients (9.5% ICU)   | AHRQ 6        |
| Dawei Wang     | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 138         | 56                | 54.3%    | 2012 KDIGO criteria         | Hospitalized Patients (26.1% ICU)  | AHRQ 8        |
| Fei Zhou       | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 191         | 56                | 62.0%    | 2012 KDIGO criteria         | Hospitalized Patients (26% ICU)    | AHRQ 8        |
| Dawei Wang     | 2020 | China, Wuhan and Huanggang | Retrospective Cross-sectional study     | 107         | 51                | 53.3%    | 2012 KDIGO criteria         | Hospitalized Patients (7.7% IMV)   | AHRQ 7        |
| Tao Chen       | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 274         | 62.0              | 62.4%    | 2012 KDIGO criteria         | Hospitalized Patients (6% IMV)     | AHRQ 8        |
| Xiaochen Li    | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 548         | 60                | 50.9%    | 2012 KDIGO criteria         | Hospitalized Patients (4.6% IMV)   | AHRQ 8        |
| Xiaobo Yang    | 2020 | China, Wuhan             | Retrospective Cross-sectional study         | 52          | 51.9              | 70%      | 2012 KDIGO criteria         | ICU Patients                       | AHRQ 7        |
| Study                  | Year | Country         | Design                     | Sample size | Age (median/mean) | Male (%) | The diagnosis criteria of AKI | Department                          | Quality score |
|------------------------|------|-----------------|----------------------------|-------------|-------------------|----------|-------------------------------|-------------------------------------|---------------|
| Yuan Yu                | 2020 | China, Wuhan    | Retrospective Cross-sectional study | 226         | 64                | 61.5%    | 2012 KDIGO criteria          | ICU Patients                        | AHRQ 7        |
| KyungSoo Hong          | 2020 | Korea, Daegu    | Retrospective Cross-sectional study | 98          | 55.4              | 38.8%    | 2012 KDIGO criteria          | Hospitalized Patients (13.3% ICU) | AHRQ 6        |
| Safiya Richardson      | 2020 | USA, New York   | Retrospective Cross-sectional study | 5700        | 63                | 60.3%    | 2012 KDIGO criteria          | Hospitalized Patients (14.2% ICU) | AHRQ 8        |
| Jamie S. Hirsch        | 2020 | USA, New York   | Retrospective Cross-sectional study | 5449        | 64.0              | 60.9%    | 2012 KDIGO criteria          | Hospitalized Patients (25.6% ICU) | AHRQ 8        |
| Jessica Ferguson       | 2020 | USA, California | Retrospective Cross-sectional study | 72          | 60.4              | 52.8%    | 2012 KDIGO criteria          | Hospitalized Patients (29.1% ICU) | AHRQ 6        |
| Matt Arentz            | 2020 | USA, Washington | Retrospective Cross-sectional study | 21          | 79                | 52%      | 2012 KDIGO criteria          | ICU Patients                          | AHRQ 8        |
| Lili Chan              | 2020 | USA, New York   | Retrospective Cross-sectional study | 3235        | 66.4              | 57.7%    | 2012 KDIGO criteria          | Hospitalized Patients (25.2% ICU) | AHRQ 8        |
Table 2

Characteristic of included studies for the incidence of AKI hospitalized COVID-19 patients using Remdesivir

| Study                  | Year | Country                                                                 | Design                                                                 | Sample size | Age (median/mean) | Male (%) | The diagnosis criteria of AKI | Department                                | Quality score |
|-----------------------|------|------------------------------------------------------------------------|------------------------------------------------------------------------|-------------|-------------------|----------|---------------------------|------------------------------------------|--------------|
| Spinello Antinori     | 2020 | Italy, Milan                                                           | Prospective, Cross-sectional study (Remdesivir)                        | 35          | 63.0              | 74.3%    | 2012 KDIGO criteria       | Hospitalized Patients (51.4% ICU)       | AHRQ 6       |
| J. Grein              | 2020 | United States, Japan, Italy, Austria, France, Germany, Netherlands, Spain, and Canada | Prospective, Cross-sectional study (Remdesivir)                        | 61          | 67                | 79%      | 2012 KDIGO criteria       | Hospitalized Patients (64.2% IMV)       | AHRQ 8       |
| J.H. Beigel           | 2020 | United States, Denmark, the United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore | RCT (Remdesivir)                                                      | 1063        | 58.9              | 64.3%    | 2012 KDIGO criteria       | Hospitalized Patients                    | Cochrane A   |
| Yeming Wang           | 2020 | China, Wuhan                                                           | RCT (Remdesivir)                                                      | 236         | 66.0              | 56%      | 2012 KDIGO criteria       | Hospitalized Patients                    | Cochrane A   |
| Jason D. Goldman      | 2020 | United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan | RCT (Remdesivir)                                                      | 397         | 62                | 64%      | 2012 KDIGO criteria       | Hospitalized Patients                    | Cochrane A   |

Incidence of AKI in hospitalized COVID-19 patients

Overall, 15135 COVID-19 patients were included in our meta-analysis.13–30 The pooled estimated incidence of AKI in all hospitalized COVID-19 patients was 12.0% (95% CI: 9.0%-15.0%, Fig. 2), and a significant heterogeneity ($I^2 = 98\%$, Chi-square = 0.19, $P < 0.01$) was observed (Table 3).

Table 3

Results of meta-analysis of the incidence of AKI in COVID-19 patients

| Study No. | COVID-19 patients No. | Proportion/OR (95%CI) | Study heterogeneity | Study heterogeneity (P value) |
|-----------|-----------------------|-----------------------|---------------------|------------------------------|
| 18        | 15135                 | 0.12 (0.09–0.15)      | 0.19                | 17                           | 98% < 0.01                    | 0.73                             |
| 5         | 981                   | 0.06 (0.03–0.13)      | 0.70                | 4                            | 86% < 0.01                    | n < 10                           |
| 2         | 696(Remdesivir) vs 600(Control) | 0.80 (0.44–1.46)    | 0                   | 1                            | 0%                            | 0.44                             | n < 10                           |
The subgroup analysis was performed according to race, age and disease severity (Supplementary Fig. 1–3). The pooled estimated AKI incidences in the Asian subgroup analysis and Western subgroup analysis are 8% (95%CI: 5%-12.0%, $I^2 = 94\%$, Chi-square = 0.62, $P < 0.01$) and 28% (95%CI: 21%-37%, $I^2 = 98\%$, Chi-square = 0.07, $P < 0.01$) respectively (Supplementary Fig. 1). At the same time, the incidence of AKI in the median/mean age more than 60 years old subgroup is 13% (95%CI: 9%-19%, $I^2 = 98\%$, Chi-square = 0.27, $P < 0.01$) comparing with 8% (95%CI: 3%-17.0%, $I^2 = 97\%$, Chi-square = 1.31, $P < 0.01$) in the median/mean age less than 60 years old subgroup. In the subgroup of more than 25% patients taken ICU/IMV in total, the AKI incidence is 24% (95%CI: 20%-29%, $I^2 = 95\%$, Chi-square = 0.05, $P < 0.01$), and the incidence of AKI in others was 6% (95%CI: 4%-11%, $I^2 = 96\%$, Chi-square = 0.58, $P < 0.01$). There was still significant heterogeneity after our subgroup analysis.

Incidence of AKI in hospitalized COVID-19 patients using Remdesivir

A total of 5 studies including 981 COVID-19 patients was to investigate the incidence of AKI in hospitalized COVID-19 patients using Remdesivir $^{10,12,31−33}$. The pooled estimated AKI incidences in hospitalized COVID-19 patients using Remdesivir (Fig. 3) was 6% (95% CI: 3%-13%) and a significant heterogeneity ($I^2 = 86\%$, Chi-square = 0.70, $P < 0.01$) was also observed (Table 3).

Remdesivir treatment does not increase the risk of AKI in patients with COVID-19

Until now, only 2 RCT were included in our study (Fig. 4) $^{10,32}$. Meta-analysis showed that comparing with COVID-19 patients without Remdesivir treatment, the Remdesivir treatment do not increase the risk of AKI in COVID-19 patients showing OR 0.80 (95%CI: 0.44–1.46, $P > 0.05$). And these two studies showed no significant heterogeneity ($I^2 = 0\%$, Chi-square = 0.0, $P = 0.44$) (Table 3).

Sensitivity analysis and publication bias

In sensitivity analysis, one by one exclusion found similar results as our study. Begger’s test was performed for the evaluation of publication bias, and no significant difference ($P > 0.05$) was detected in the analysis of incidence of AKI in all hospitalized COVID-19 patients. Less than 10 of study number is not enough for the publication bias calculation in the analysis of incidence of AKI in hospitalized COVID-19 patients using Remdesivir for treatment.

Discussion

In this meta-analysis, results from 18 retrospective cross-sectional studies including 15135 patients hospitalized with COVID-19 from January 1, 2020 to June 1, 2020 demonstrated that AKI was not rare in COVID-19. The incidence of AKI is associated with the age, disease severity and race of patients in our subgroup study. And we also proved that using Remdesivir for treatment did not increase the risk of AKI.

COVID-19 infection is primarily a respiratory disease, but other organs including the kidneys are often involved. Renal abnormalities, such as proteinuria, hematuria, and AKI occurred in patients with COVID-19 $^{34}$. AKI is characterized by a rapid increase in serum creatinine, decrease in urine output, or both $^{35}$. The currently widespread AKI definition was developed by the Kidney Disease Improving Global Outcomes (KDIGO) group in 2012 $^{36}$. The most common causes of AKI were septic shock, post major surgery, cardiogenic shock, drug toxicity and hypovolemia $^{37}$. The cause of AKI in COVID-19 is likely to be multifactorial, including hemodynamic instability, microcirculatory dysfunction, tubular cell injury, renal congestion, microvascular thrombi and endothelial dysfunction $^{38}$. Pathology from autopsies of patients with COVID-19 with renal failure revealed that the kidneys had varying degrees of acute tubular necrosis, diffuse proximal tubule injury with the loss of brush border, non-isometric vacuolar degeneration, hemosiderin granules and pigmented casts $^{39,40}$. We found out that incidence of AKI in all hospitalized COVID-19 patients was 12.0%. The diversity of patients included in our meta-analysis cause the heterogeneity. According to the subgroup analysis, the estimated AKI incidence of patients with averaged age more than 60 years old is higher than patients averaged age less than 60 years old (13% vs 8%). Many reports on COVID-19 have highlighted age-related differences in health outcomes, mortality of COVID-19 is particularly high among older patients $^{41,42}$. Age is also an important risk factor for AKI $^{43}$. The pooled estimated AKI incidences in the Asian subgroup was lower than Western subgroup (8% vs 28%). Black race is a risk factor for AKI $^{44}$. In a large cohort study of hospitalization COVID-19 patients among black patients and white patients with COVID-19, 76.9% of the patients who were hospitalized with COVID-19 and 70.6% of those who died were black, whereas blacks comprise only 31% of the population $^{45}$. The incidence of AKI in ICU patients with the COVID-19 was particularly high range from 8%-62% $^{15,18,23−25,28,29}$. Critical ill patients...
hospitalized with COVID-19, requiring ventilator is more likely to develop AKI\(^4\). In our subgroup study, patients were divided into two groups according to the proportion of using ventilator or ICU. The incidence of AKI is higher in more severe patients (24\% vs 6\%).

As the ongoing pandemic of COVID-19, there is an urgent need to identify safe and effective treatment options, such as antiviral drug. Introduction of antiviral drugs is a common cause of drug-induced AKI\(^{46,47}\). In the clinical experiment of Remdesivir, AKI as the most frequent adverse event lead to drug discontinuation\(^{11,12}\). Antiviral drugs cause AKI by many mechanisms including direct renal tubular toxicity, allergic interstitial nephritis, and crystal nephropathy\(^{48,49}\). But in animal models, Remdesivir treatment was effective against MERS-CoV and did not show any side effect of AKI\(^50\). As shown in Figs. 2 and 3, the incidence of AKI in hospitalized COVID-19 patients using Remdesivir is lower than all hospitalized COVID-19 patients whether using Remdesivir or not. The meta-analysis of RCTs also proved that Remdesivir did not increase the risk of AKI in hospitalized COVID-19 patients. Similar to the results of our study, a RCT study of Ebola virus disease (EVD) therapeutics also showed that Remdesivir reduced mortality from EVD without increase the risk of AKI\(^7\). Our meta-analysis may provide an evidence for future study that AKI is associated with the natural cause of COVID-19, not the adverse event after the usage of the drug.

Our meta-analysis had some limitations. First, most of the studies included in were retrospective cross-sectional study, although most of them (72\%) were high quality. The RCTs included in our study were high quality but with limited amount. Sensitivity analysis which performed using one by one exclusion got similar results in our study. Second, there was a statistically significant heterogeneity in the meta-analysis of AKI incidence. The diversity of included studies involving different disease stage or activity, age, race and sex might be associated with the heterogeneity. Although we did subgroup study, the results still had significant heterogeneity. Third, the limited original studies (n=10) for the meta-analysis of the incidence of AKI in hospitalized COVID-19 patients using Remdesivir. No begger’s test is needed. Finally, since the clinical experiments for Remdesivir are ongoing now, the extra clinical data should be considered after their publications.

**Conclusion**

AKI was common in hospitalized COVID-19 patients and the incidence of AKI was associated with age, disease severity and race. At the same time, Remdesivir treatment does not increase the risk of AKI in hospitalized COVID-19 patients. Our meta-analysis may provide an evidence for future study that AKI is associated with the natural cause of COVID-19, not the adverse event after the usage of the drug.

**Abbreviations**

AKI
acute kidney injury
SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2
EVD
Ebola virus disease
RCTs
Randomized controlled trials

**Declarations**

**Consent for publication**

Not applicable.

**Authors’ 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.
All authors have read and approved the manuscript.

**Competing Interests**

The authors declare that they have no competing interests.

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**Availability of data and material**

All data generated or analysed during this study are included in this published article.

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**Figures**

Figure 1

Flow diagram of studies identified, included, and excluded.
Figure 2

Forest plot and meta-analysis of incidence of AKI in hospitalized COVID-19 patients.

Figure 3

Forest plot and meta-analysis of AKI incidences in hospitalized COVID-19 patients using Remdesivir.
Figure 4

Forest plot and meta-analysis of AKI incidences in hospitalized COVID-19 patients using Remdesivir of 2 RCT studies.

### Supplementary Files

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- PRISMA2009checklist.doc