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Original Article

A Meta-Analysis of Association between Remdesivir and Mortality among Critically-Ill COVID-19 Patients

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ABSTRACT

Background: The World Health Organization guidelines did not make a recommendation on use of remdesivir based on disease severity. Little is known regarding effectiveness of remdesivir in critically ill coronavirus disease 2019 (COVID-19) patients. This has led to a state of dilemma for doctors leaving them skeptical of whether they should continue to recommend the drug or not.
Materials and Methods: A systematic search adhering to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines was conducted from inception until February 20, 2020. Electronic bibliographic databases (PubMed, Cochrane database, Scopus, Embase) were included. Using dichotomous data for select values, the unadjusted odds ratios (ORs) were calculated applying Mantel Haenszel (M-H) using random-effects model. The primary outcome of interest was all-cause mortality in ventilated and non-ventilated patients.
Results: The Remdesivir arm was associated with similar rates of 28-day all-cause mortality (OR: 0.93, 95% confidence interval [CI]: 0.80 - 1.08; $P = 0.33$). Remdesivir was not found to be favorable for ventilated patients. Non ventilated COVID-19 patients showed a significant lower in-hospital mortality rate as compared with patients requiring mechanical ventilatory support (OR: 6.86, 95% CI: 5.39 - 268.74; $P < 0.0001$).
Conclusion: Non-ventilated patients were associated with significant lower all-cause mortality rates. Prudent use of remdesivir is recommended in critically ill COVID-19 patients.

Keywords: Remdesivir; COVID-19; Critical care; Antiviral therapy

INTRODUCTION

In the light of the current coronavirus disease 2019 (COVID-19) pandemic, we still stand at odds regarding a perfect strategy to mitigate its adverse clinical progression. Several antiviral agents like remdesivir and favipiravir have been investigated for increasing survival of COVID-19 patients. Remdesivir has been repurposed in an effort to improve the survival of

Conflicts of interest
No conflicts of interest.

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Conceptualization: AAR. Data curation: DMRC. Formal analysis: AAR. Investigation: AAR, DMRC. Methodology: AAR, DMRC. Project administration: AAR, ALM. Software: AAR, ALM. Supervision: AAR. Validation: AAR, GE, SK. Visualization: AAR, SAH, SKRP, GE, SK, ALM. Writing - original draft: AAR, SAH, SKRP, GE, ALM, SAR. Writing - review & editing: AAR, SAH, SKRP, GE, SK, SAR.

COVID-19 patients. It is an investigational adenosine analogue developed for the treatment of Ebola virus (EBOV) but failed to meet efficacy endpoints in a randomized trial conducted during an Ebola outbreak [1]. Upon intracellular uptake it metabolizes into an active nucleoside triphosphate and incorporates in to viral RNA and interferes with downstream viral RNA-dependent RNA polymerase function [1]. It further disrupts viral exoribonuclease activity and inhibits viral replication [1]. It is the first drug to attain emergency US Food and Drug Administration (FDA) approval for the treatment of coronavirus [2]. However, the emergence of conflicting results from the WHO COVID-19 SOLIDARITY trial has led to uncertainty regarding its efficacy [3]. This has led to a state of dilemma leaving them skeptical regarding its repercussions on clinical care and whether they should continue to recommend the drug or not.

MATERIALS AND METHODS

1. Search strategy and selection

A systematic search adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was performed (**Fig. 1**) [4]. Online bibliographic databases PubMed, Embase, and Scopus were included. No date restrictions existed wherein the search was conducted from inception until the February 20, 2021. Using Boolean logic, a combination of MeSH terms "Remdesivir", "COVID-19", "All-cause mortality", "ventilated", "non-ventilated", "anti-viral", "respiratory support", were used to conduct a comprehensive search in the above-mentioned databases. A cross-reference check of previously published meta-analysis on this topic was also performed.

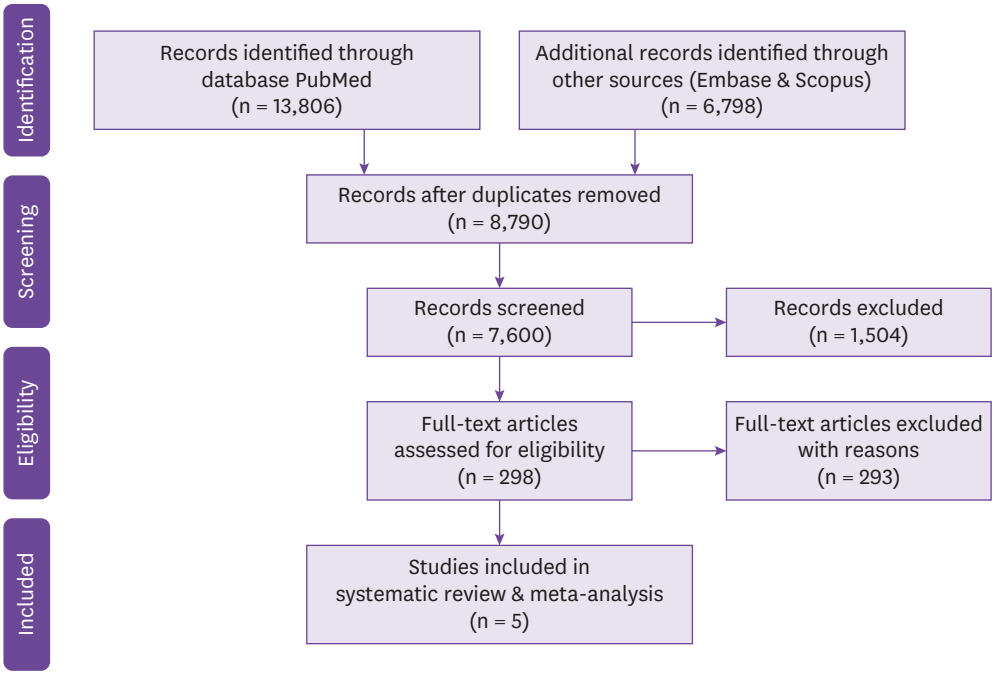

Figure 1. PRISMA flow of the search strategy for systematic review and meta-analysis on remdesivir *vs.* placebo for the management of COVID-19.

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2. Inclusion criteria

Studies included were required to meet the following specifications: (1) >10 COVID-19 patients were enrolled (2) Adult patients (age ≥18 years) who had COVID-19 pneumonia and positive test samples with outcomes for intervention of Remdesivir including clinical improvement and its safety.

3. Exclusion criteria

Studies that had insufficient data, systematic reviews, meta-analyses, letters, editorials, case reports, conference abstracts and case series with less than 10 patients (total n = 1,504) were also excluded.

4. Data extraction and quality assessment

Information regarding the study design, demographic characteristics, and various outcomes were extracted. No language restrictions were made. All duplicates were removed using Endnote X9 (18th ed, Lea & Febiger, Philadelphia, PA, USA) by two independent reviewers (AAR and SAH). Titles and abstracts of all articles from the initial search were independently screened by two authors (AAR and SAH). Any discrepancies concerning the evaluation of the studies were arbitrated by the senior author. Studies were also screened by searching reference lists of included studies (backward snowballing).

5. Study definitions and endpoints

The primary outcome of interest was in-hospital mortality within subgroups based on respiratory support. The secondary efficacy endpoints were (1) 28 day all-cause mortality (2) any grade >3 adverse events and (3) serious adverse events.

6. Statistical Analysis

Statistical analyses were performed using the Cochran-Mantel Haenszel method under the random-effects model to calculate unadjusted risk ratios (RR) for the primary and secondary endpoints. The estimated effect size was reported as a point estimate and 95% confidence interval (CI). An alpha criterion of *P*-value ≤0.05 was considered statistically significant. The Higgins's I-squared (I^2) statistical model was used for assessment of study heterogeneity, with values<25%, 25 - 50%, 50 - 75%, and>75% corresponding to no, low, moderate, and high degrees of heterogeneity, respectively. A CI of 95% and a *P*-value <0.05 were used in all our analyses and to assess for statistical significance. Statistical analyses were performed using the Cochrane review manager (RevMan) version 5.4 (The Cochrane Community, London, UK).

RESULTS

In our meta-analysis, a total of five studies were analyzed [3, 5-8]. More specifically we analyzed the association between Remdesivir use and in-hospital mortality within subgroup based on respiratory support, 28 day all-cause mortality, any grade >3 adverse events and serious adverse events. Remarkably, non-ventilated COVID-19 patients showed a significant lower in-hospital mortality rate when compared with patients requiring mechanical ventilation [OR: 6.86, 95% CI: 5.39 - 8.74, *P* <0.00001] (**Fig. 2**). The Remdesivir arm also demonstrated similar rates of 28-day all-cause mortality (OR: 0.93, 95% CI: 0.80 - 1.08, *P* = 0.33) (**Supplementary Fig. 1**)-and any grade >3 adverse events (OR: 0.68, 95% CI 0.64 - 1.00, *P* = 0.05) (**Supplementary Fig. 2**). However, when compared to placebo, Remdesivir was also associated with less serious adverse

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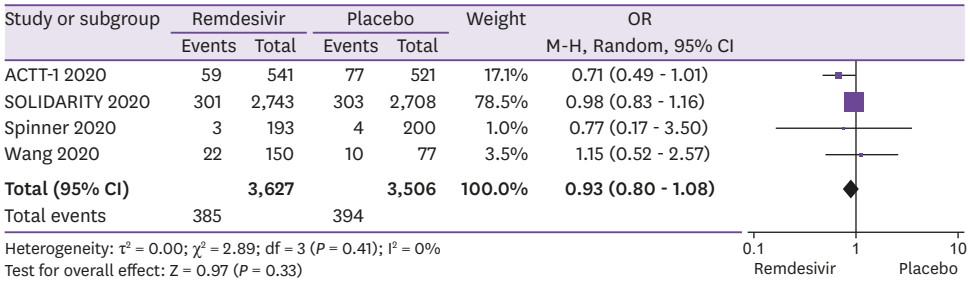

Figure 2. Association between remdesivir and in-hospital mortality within subgroup based on respiratory support.

events (OR 0.68, 95% CI: 0.53 - 0.86 $P = 0.001$) (**Supplementary Fig. 3**). Finally, we also report no significant heterogeneity among the studies ($I^2 = 0$).

DISCUSSION

The current study differs from previous meta-analyses in that it examined the efficacy of remdesivir within subgroups based on respiratory support and severity of COVID-19 subgroups.

Based on our analysis, our results re-iterate that non-ventilated patients were associated with significant lower all-cause mortality rates. Remdesivir use was not found to be favorable for patients requiring ventilation support.

Although remdesivir was the first drug to get Emergency FDA authorization as a potential treatment for COVID-19, it is still under investigation in selected patient groups due to conflicting data from trials [3, 5, 8]. In particular, testing whether remdesivir is beneficial in critically ill patients is of extreme interest.

These findings from the current meta-analysis are in concordance with the recent results of a study including a cohort of mechanically ventilated patients. The study stated that although remdesivir was associated with accelerated rate of recovery, it was not associated with a significant reduction of mortality [9].

Furthermore, remdesivir administration demonstrated no significant difference in rates of 28-day all-cause mortality, irrespective of subgroups based on severity. More recently, the American College of Physicians has also amended the clinical guidelines regarding the use of remdesivir in patients receiving mechanical ventilation due to its inadvertent associated net increase in mortality in critically ill patients [10]. This sets up a precedent for the prudent use of remdesivir in critically ill COVID-19 patients.

Furthermore, the European Society of Intensive Care Medicine has recently advised against remdesivir for sickest COVID-19 patients discouraging its use in intensive care units.

In a recent interview, the president of the European Society of Intensive Care Medicine, Dr. Jozef Kesecioglu has advised against routine use of remdesivir for critically ill COVID-19 patients and further discouraged its routine use in intensive care units [11].

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Furthermore, our study also highlights the need to start antiviral before the disease causes progression to mechanical ventilation. There is a possibility of patients being hospitalized late, which could diminish the efficacy of the drug.

Given its antiviral mechanism, it seems to benefit when the virus is in the blood and should be used only for mild to moderate COVID-19 patients to decrease the viral load. Approaches that target the virus (passive immunity, antivirals, interferons) may have more impact in early course of infection. In critical COVID-19 patients, the disease's inflammatory impact becomes the more significant factor to address. Steroids douse the fire when the inflammatory process begins. Approaches that modulate the immune response (dexamethasone, baricitinib, tocilizumab) are more likely to work later in the disease course. According to the latest Phase III COV-BARRIER sub study, Baricitinib alone was associated with significant lower mortality risk in mechanically ventilated COVID-19 patients or those receiving extracorporeal membrane oxygenation (ECMO) [13]. Therefore, it is logical to extend the use of remdesivir during the early stages before the complications of immune system lead to impaired organ function and widespread inflammation.

Based on our meta-analysis of major clinical studies, we firmly believe and meet eye-to-eye on Dr. Josef's upcoming recommendation. These findings support Dr. Josef's recommendation discouraging the use of routine remdesivir for mechanically ventilated critically ill patients.

Nonetheless, with mortality data less convincing, broad use beyond its ideal patients is plausible, straining the supply of the drug. Hence, there needs to be extra consideration for prescribing remdesivir to the right patients, not just to ensure benefit but also the supply rate.

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SUPPLEMENTARY MATERIALS

Supplementary Figure 1
Association between remdesivir and 28-day all-cause mortality.

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Supplementary Figure 2
Association between remdesivir use and grade >3 adverse events.

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Supplementary Figure 3
Association between remdesivir and its use associated adverse events.

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