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Review Article

# Remdesivir for the Treatment of Severe SARS-CoV-2 (COVID-19): A Systematic Review and Meta-Analysis

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ABSTRACT

**Background:** Coronavirus Disease in 2019 (COVID-19) is a pandemic caused by SARS-CoV-2 infection. Over 53 million people have been infected with over 1.3 million deaths. However, there is no standard treatment or vaccines to date. Recently, several randomized controlled trials and cohort studies have demonstrated the efficacy of remdesivir for the treatment of severe COVID-19 patients. This is a systematic review and meta-analysis to define its efficacy.

**Methods:** A systematic review was done on databases (PubMed, Embase, Medline, Cochrane) on 9 Nov 2020. Search keywords were remdesivir, COVID-19, SARS-CoV-2, randomized controlled trials and cohort studies. Studies with high-evidence values were selected to evaluate its clinical efficacy in terms of risk ratio, time to clinical improvement, and mortality risk. Subgroup analysis was performed based on baseline hospitalization status, age and ethnicity.

**Results:** Of the 1328 studies, 6 studies were selected and pooled for meta-analysis. Remdesivir was associated with clinical improvement (risk ratio 1.14, 95% CI 1.02-1.28, p=0.02). It shortened the mean time of clinical improvement by 3.32 days (95% CI -4.37 to -2.28, p<0.001). However, its use was not associated with reduced mortality risk (risk ratio 0.75, 95% CI 0.40–1.40). In subgroup analysis, remdesivir was associated with clinical improvement in patients without the need of invasive ventilation (risk ratio 1.90, 95% CI 1.58-2.29, p<0.001; hazard ratio 2.22, 95% CI, 1.64-3.02), and age less than 70 years (risk ratio 2.14, 95% CI 1.39-3.28, p<0.001).

**Conclusion:** Remdesivir is effective in the treatment of severe COVID-19 patients, in particular those without invasive ventilation.



## Introduction

Coronavirus Disease in 2019 (COVID-19) has been declared as a pandemic. It has spread to over 200 countries and has infected over 53 million people, with over 1.3 million deaths as of 17 November 2020 [1]. COVID-19 is caused by SARS-CoV-2 infection, which is a positive-sense, single-stranded RNA virus. The incubation period is 1-14 days. It is transmitted mainly through droplets and close contact. A mild infection is self-limiting, but 19% of the patients will have severe infection with a high risk of death [2]. Currently, there is no standard treatment or vaccines.

Remdesivir (GS-5734) is an RNA-dependent RNA polymerase inhibitor, which has been used as an antiviral in Ebola and Marburg virus

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infection, with effective outcomes [3]. Preliminary studies have shown a promising effect in fighting against severe COVID-19 infections. Its therapeutic effects, adverse events and usage in COVID-19 patients are currently being explored in large-scale randomized controlled trials (RCTs). A recent meta-analysis in a preprint format has only included two RCTs [4]. We aimed to provide a more up-to-date systematic review and meta-analysis to investigate the therapeutic effect and adverse events of remdesivir in severe COVID-19 infections with existing literature to date.

## Methods

A systematic search was performed on databases (PubMed, Embase, Medline, Cochrane) on 9 November 2020. The keywords were remdesivir, COVID-19, and SARS-CoV-2, randomized controlled trial, cohort study. The inclusion criteria were full English papers with high evidence value: only cohort studies and randomized controlled trials were included. All patients were laboratory-confirmed SARS-CoV-2 infections with PCR testing. They had a severe infection (see below) at baseline. The primary outcome of interest was the composite outcome of improved clinical prognosis. The secondary outcome of interest were serious adverse events. Serious adverse events are defined as any untoward medical occurrence that at any dose may result in significant disability/incapacity, which require intervention to prevent permanent impairment and prolonged inpatient hospitalization. Subgroup analysis was performed according to baseline ordinal score, age and races on clinical outcomes in COVID-19 patients receiving remdesivir.

All studies fulfilling the following criteria were selected and analysed. The inclusion criteria were 1) peer-reviewed English article with clinical data; 2) high-quality evidence, including cohort studies and RCTs, and 3) adult severe COVID-19 patients with laboratory confirmation, and either an oxygen saturation of 94% or less while breathing ambient air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300mmHg or less. The titles, abstracts and full articles were independently screened by two authors (ZY and KSC). Duplicate articles were removed, and reasons for exclusions are documented in the table in the appendix.

### Data Extraction and Bias Assessment

Data extraction was performed by ZY and KSC with a specific focus on study design, population demographics, therapeutic outcomes, and serious adverse events. Bias assessments were performed by the Cochrane collaboration tool for RCT, and the Newcastle-Ottawa Scale for cohort studies. (See supplementary materials in appendix) Bias or quality issues were minimized by cross-checking between the authors.

To standardize the ordinal score based on the oxygenation status for measurement of clinical outcome, the eight-category scale is adopted in this review. Clinical improvement was defined as patients improving to a category of 1,2 or 3 from a more severe category or decreasing by at least 2 points from baseline on the ordinal scale. The eight-category ordinal scale was defined as follows: 1) not hospitalized, no limitations of activities; 2) not hospitalized, limitation of activities, home oxygen requirement or both; 3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization is extended for infection-control reasons); 4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19-related or other medical conditions); 5) hospitalized, requiring any supplemental oxygen; 6) hospitalized, requiring non-invasive or use of high-flow oxygen devices; 7) hospitalized, receiving invasive mechanical ventilation of extracorporeal membrane oxygenation (ECMO) and 8) death.

Review manager, version 5.3, SPSS (IBM), and Microsoft Excel 2016 were used in data analysis. Dichotomous data were pooled in a random-effect model as risk ratio while cumulative time-to-clinical-improvement data were pooled as hazard ratio using the generic inverse-variance method with 95% confidence interval. Data reported in median and inter-quartile range were converted to median and standard deviation by the method introduced by Hozo *et al.* [5]. Hazard ratio reported in 95% confidence interval was pooled as weighted hazard ratio with mean and standard error. The random-effects model was used as the main analysis. Heterogeneity was assessed using $I^2$ index and chi-square ($\chi^2$) test, with p-value smaller than 0.1 as statistically significant. As there are a limited number of studies, assessment of publication bias by Egger's test for funnel plot asymmetry was not performed.

## Results

As of 9 Nov 2020, 1328 studies were retrieved from the databases. After screening of titles and abstracts, 9 articles were identified for full-text review. Following the PRISMA guidelines in PRISMA flow diagram, the study profile is shown in (Figure 1). Eventually, 6 articles were selected for meta-analysis (Table 1). Three articles were excluded: one study is a case report; the second is a cohort study on pregnant women with poly-pharmacy, and the therapeutic effects of remdesivir are not conclusive; the third one is a randomized controlled study with a specific focus on patients with moderate COVID-19 infection [6].

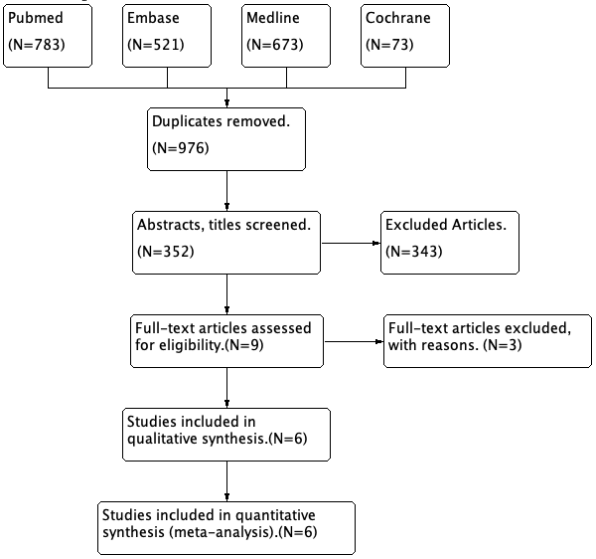


**Figure 1:** PRISMA flow chart for the pooled studies. Articles were screened and excluded due to review (N=181), without primary therapeutical data (N=151), protocol (N=4), guideline (N=4), and foreign language writing (N=3). Full-text articles were excluded since one study is a case report, the second one is a cohort study on pregnant women with polypharmacy and the therapeutic effects of remdesivir are not conclusive. The third study focused on patients with moderate COVID-19 infections.

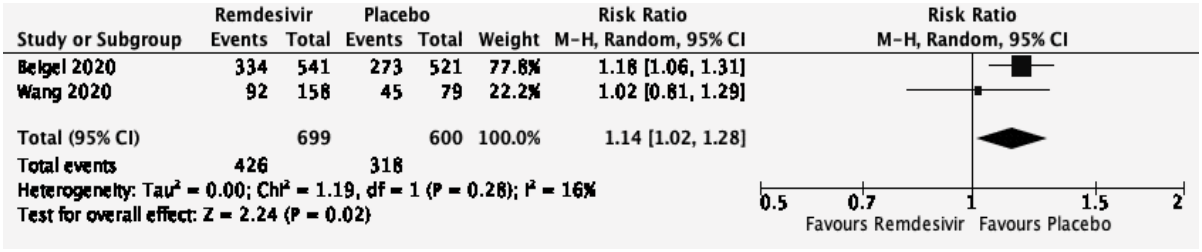


**Figure 2A:** Forest plot for risk ratio of clinical improvement in pooled studies.

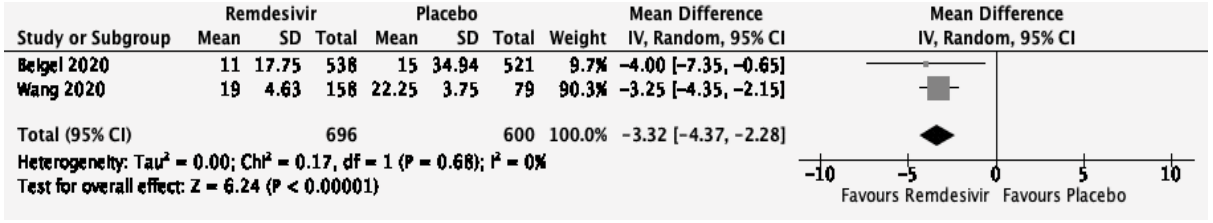


**Figure 2B:** Time to clinical improvement difference in pooled studies.

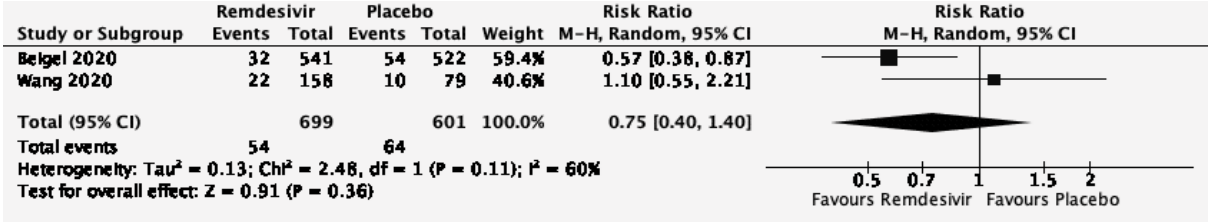


**Figure 2C:** Forest plot for mortality risk in pooled studies.

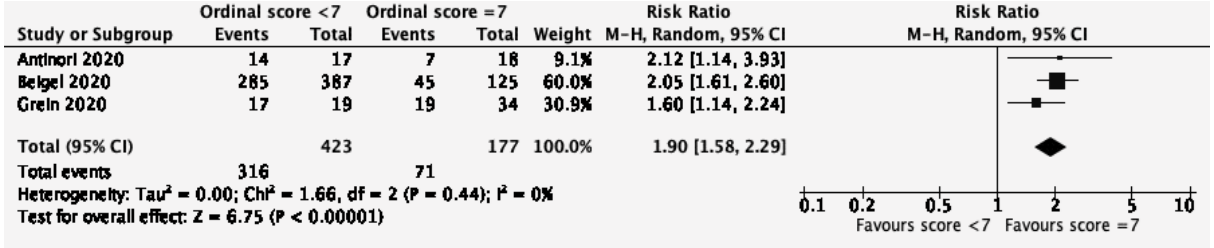


**Figure 3A:** Subgroup baseline ordinal score of 7 analysis in remdesivir group for clinical improvement.

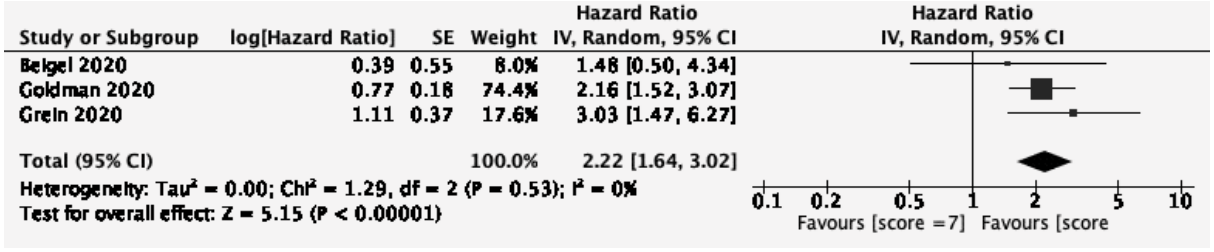


**Figure 3B:** Subgroup analysis of hazard ratio of clinical improvements in remdesivir group with regard to their baseline condition.

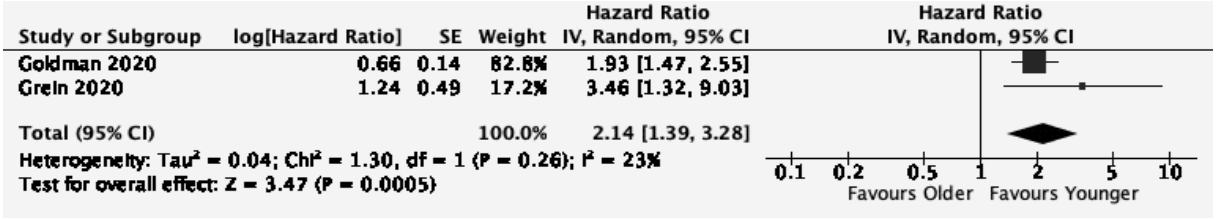


**Figure 3C:** Subgroup age analysis in remdesivir group for clinical improvement.

Of the 1,793 patients from the 6 selected studies, the mean age was 60.6 years. Remdesivir increased the chance of clinical improvement compared with placebo (risk ratio 1.14, 95% CI 1.02-1.28, p=0.02); but it is not associated with a reduction of mortality (risk ratio 0.75, 95% CI 0.40-1.40, p=0.36). Remdesivir shortened the mean time of clinical improvement by 3.32 days (95% CI -4.37 to -2.28, p<0.001). Figure 2 shows the clinical prognosis and adverse events of the pooled studies.

**Table 1:** Summary of the studies included.

| No. | References | Study design | Population | Mean age & Sample size | Intervention & number of patients | Control & number of patients | Findings |
|---|---|---|---|---|---|---|---|
| 1 | Beigel *et al.* [7, 8] | Phase 3, multi-centre, randomised, double blind, placebo-controlled trial | Severe COVID-19 patients.<br><br>684 males<br>379 females<br><br>Race – no. (%)<br>White: 565 (53.2)<br>Black: 219 (20.6)<br>Asian:134 (12.6)<br>American Indian: 7(0.7)<br>Others/unknown: 138(13.9) | 58.9 years<br>&<br>1063 patients | -Intravenous remdesivir 200-mg loading dose on day 1, followed by a 100-mg maintenance dose daily on day 2 through 10, or until hospital discharge or death.<br><br>-541 patients. | -Placebo with normal saline in European countries; while opaque bag or tubing covered infusion in non-European countries.<br><br>-522 patients. | -Patients in remdesivir group had a shorter time to recovery than placebo group.<br>(median 11 days, compared with 15 days; rate ratio for recovery, 1.32; 95% CI 1.12 to 1.55, P<0.001)<br><br>-Lower estimated mortality in remdesivir group (7.1%) than placebo group (11.9%) on day 14. Hazard ratio for death was 0.70, 95% CI, 0.47 to 1.04)<br><br>-607 recovered patients (57%), with 334 in remdesivir group (31%) and 273 in placebo group (26%).<br><br>-Comparable percentage of severe events in both groups. (Remdesivir group 21.1% vs placebo group 27.0%)<br><br>-Fewer deaths in remdesivir group (32 deaths) than placebo group (54 deaths) by day 14 |
| 2 | Goldman *et al.* [9] | Multi-centre, open-labelled randomised controlled trial | Severe COVID-19 patients.<br><br>253 males<br>144 females<br><br>Race – no. (%)<br>White: 276 (69.5)<br>Black: 44 (11.1)<br>Asian: 45 (11.3)<br>Others: 27 (6.8) | 61.5 years<br>&<br>397 patients | -Intravenous remdesivir 200mg on day 1, then 100mg daily from day 2 to 5 once daily.<br><br>-200 patients. | -Intravenous remdesivir 200mg on day 1, then 100mg daily from day 2 to 10 once daily.<br><br>-197 patients. | -No significant difference between a 5-day course and 10-day course in patients with COVID-19 not requiring mechanical ventilation.<br><br>-Clinical improvement in 5-day course group (65%) is comparable to 10-day course group (54%), p=0.14.<br><br>-Median time to recovery in 5-day-course group is 10 days (IQR 6-18 days); while the median time for 10-day-course group is 11 days (IQR 7 days- days not possible to estimate).<br><br>-Higher discharge rate in 5-day-course group (60%) than the 10-day-course group (52%)<br><br>-Lower mortality rate in 5-day-course group (8%) than the 10-day-course group (11%). |
| 3 | Grein *et al.* [10] | Multi-centre prospective cohort study | Severe COVID-19 patients.<br><br>27 males<br>34 females<br><br>Region of recruitment | 64.0 years<br>&<br>61 patients | -Intravenous remdesivir 200mg on day 1, then 100mg daily from day 2 to 10 once daily.<br><br>-61 patients. 34 patients receiving invasive ventilation | No control arm. | -Cumulative incidence of clinical improvement was 84% by day 28, 95% CI 70-99 by Kapalan-Meier analysis.<br><br>-Less frequent clinical improvement in patients receiving invasive ventilation than those with non-invasive ventilation. (Hazard ratio for improvement, 0.33; 95% CI 0.16 – 0.68) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | no. (%):<br>US: 22 (42)<br>Japan: 9 (17)<br>Europe/Canada:<br>22 (42) | | and 19 receiving non-invasive ventilation. | | -7 deaths (13%).<br><br>-25 patients (41%) were discharged.<br><br>-32 patients (60%) reported of adverse events, with 12 patients (23%) having its serious form. |
| 4 | Wang *et al.* [18] | Multi-centre, randomised, double blind, placebo-controlled trial | Severe COVID-19 patients.<br><br>89 males<br>69 females<br><br>Ethnicity composition unspecified. The trial took place in China. | 65.3 years<br>&<br>237 patients | -Intravenous remdesivir 200mg on day 1, then 100mg daily from day 2 to 10 once daily.<br><br>-158 patients. | -Placebo infusion of same volume provided by Gilead Sciences for 10 days<br><br>-79 patients. | -No significant difference of median time to clinical improvement between remdesivir grop (21.0 days, IQR=13.0 – 28.0 days) and placebo group (23.0 days, IQR = 15.0 – 28.0 days). Hazard ratio was 1.27, 95% CI, 0.89 – 1.80 without statistical significance.<br><br>-Comparable mortality between remdesivir group (22 patients [14%]) and placebo group (10 patients [13%])<br><br>-137 discharged patients (58%), with 92 in remdesivir group (39%) and 45 in placebo group (19%).<br><br>-Numerically faster median time to clinical improvement in remdesivir group (18.0 days, IQR=12.0 – 28.0 days) vs placebo group (23.0 days, IQR=15.0 – 28.0); Hazard ratio 1.52, 95% CI 0.95-2.43)<br><br>-No significant difference in viral load of both upper and lower respiratory specimens since day 5 between 2 groups.<br><br>-Percentage of severe events was comparable in both groups. (Remdesivir group 66% vs placebo group 64%) |
| 5 | Antinori *et al.* [20] | Single-centre, open-labelled prospective cohort study | Severe COVID-19 patients.<br>26 males<br>9 females<br><br>Ethnicity composition unspecified. The trial took place in Milan, Italy in March 2020. | 63.0 years<br>&<br>35 patients | -Intravenous remdesivir 200mg on day 1, then 100mg daily from day 2 to 10 once daily.<br><br>-35 patients. 18 in Intensive Care Unit (ICU), while 17 in Infectious Disease Ward (IDW). | No control arm | -Higher proportion of patients with improved hospitalization status in IDW cohort (88.2%) than ICU cohort (38.9%) by day 28.<br><br>-22 patients had a negative viral load after a median of 12 days (IQR 9.25 – 16.75) of initiation of remdesivir.<br><br>-20 patients (57%) were discharged, with 14 (40%) from ICU and 6 (17%) from IDW.<br><br>-8 treatment discontinuations due to adverse events. |

Subgroup analysis of remdesivir group based on baseline ordinal score of 7 showed that remdesivir favoured clinical improvement in patients with a baseline score of less than 7, i.e., without the need of invasive ventilation (risk ratio 1.90, 95% CI 1.58-2.29, p<0.001) (Figure 3A). As shown in (Figure 3B), the chance of clinical improvement was higher in patients with baseline score less than 7 (hazard ratio 2.22, 95% CI, 1.64-3.02, p<0.001). Less than half of the patients receiving invasive ventilation and remdesivir showed clinical improvements. Younger patients had a better chance of clinical improvement compared to older patients (hazard ratio 2.14, 95% CI 1.39-3.28, p<0.001) (Figure 3C). The cutting point of young and old is 65 years old in the studies by Beigel *et al.* and Goldman *et al.*; while the cutting point is 70 years old in the study by Grein *et al.* [7-10].

Subgroup analysis of races could not be performed. Goldman *et al.* reported that compared with Asians, the hazard ratio of time to clinical improvement in the Black and White populations were 3.80 (95% CI 2.28-6.35) and 2.45 (95% CI 1.60-3.76), respectively. Beigel *et al.* reported that the recovery rate ratio in the Black, White and Asian populations were 1.14 (95% CI 0.81-1.61), 1.39 (95% CI 1.12-1.73) and 1.04 (95% CI 0.68-1.57). There is a trend in both studies for the Black and White populations to have better recovery time/rate compared with the Asian population. However, pooled data showed uncertainty because the 95% confidence interval included the null value, and therefore it did not reach statistical significance. Serious adverse events are documented in the appendix. The serious adverse event rate was 20.1% in the treatment group and 23.8% in the placebo group. Of the 383 serious adverse events in the pooled studies, 228 (59.5%) serious adverse events were reported related to the respiratory system.

**Discussion**

The systematic review and meta-analysis evaluated the improvement of prognosis by remdesivir in the treatment of severe COVID-19 patients. All studies included are of high evidence value. Even though the evidence is limited to date, it is likely that remdesivir is effective in treating patients with severe COVID-19, in particular those without the need for invasive ventilation. Remdesivir is an RNA-dependent RNA polymerase inhibitor that was first shown to be effective in the treatment of COVID-19 *in vitro* and in some case reports [11, 12]. It was then adopted for compassionate use and emergency use globally, with preliminary reports showing promising outcomes in the treatment of severe COVID-19 patients [7]. However, large scale double-blinded randomized controlled trials are required to validate its efficacy and safety. Since remdesivir monotherapy is not very effective for COVID-19 patients with invasive ventilation and old age groups, combination therapy is required.

Remdesivir is an effective treatment for severe SARS-CoV-2 infection. It reduced median clinical improvement time by 3.32 days. This is consistent with the study by Ferner *et al.* because remdesivir reduces viral RNA production by the evasion of exoribonuclease, and it interferes with viral RNA-dependent RNA polymerase [13]. Subgroup analysis of baseline hospitalization status showed that the status of ventilation is an indicator for their therapeutic responses to remdesivir. Patients with baseline non-invasive ventilation had more significant clinical improvement than those with invasive ventilation (risk ratio 1.90, 95% CI 1.58-2.29, p<0.001; hazard ratio 2.22, 95% CI, 1.64-3.02). The possible reason may be due to the irreversible diffuse alveolar damage and hyaline formation in severe and critically ill patients [14].

The age of patients plays a vital role in therapeutic response to remdesivir. Within remdesivir group, younger patients had a higher chance of clinical (hazard ratio 2.14, 95% CI 1.39-3.28, p<0.001). Grein *et al.* showed that patients with age under 70 years of age had a higher cumulative chance of clinical improvement rate (near 90%) than over 70 years (60%) [10]. Beigel *et al.* further showed that the rate recovery ratio in adult patients younger than 40 years old (2.03, 95% CI 1.31-3.15) was nearly doubled than those older than 40 years (40 to 64 years old: 1.16, 95% CI 0.94-1.44; older than 64-years-old: 1.37, 95% CI 1.02-1.83) [7, 8]. The result is consistent with a meta-analysis by Cohen *et al.*, who showed that over 80% COVID-19 deaths in Europe were elderly patients older than 70 years old [15].

Whether remdesivir favours clinical improvement in the Black and the White populations, compared with Asians, remains uncertain. Goldman *et al.* showed that the black and the white populations had a higher chance of clinical recovery when receiving remdesivir, compared with Asians [9]. Beigel *et al.* showed that the recovery rate ratio of Black and Asian populations were 1.14 (95% CI 0.81-1.61 and 1.04 (95% CI 0.68-1.57), respectively [7, 8]. It has been postulated that non-Asians may have a higher chance of clinical improvement due to the lower levels in angiotensin-converting enzyme 2 (ACE2) expression [16]. ACE2 is the host cell receptor responsible for mediating with S-protein of SARS-CoV-2 for viral entry. A meta-analysis of six studies on the effect of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in COVID-19 patients shows that reduction of ACE2 expression correlates with a 43% reduction in odds of death in those patients taking ACEI or ARB.

However, the WHO report showed that the overall death rate and infection cases outside Asia are higher than that in Asia [1]. This may be related to the availability of health-care resources to the public. In a study of the association between health-care resources availability and COVID-19 mortality during early outbreak, Ji *et al.* concluded that the lower mortality outside Wuhan province in China was due to a higher health-care resources availability outside Wuhan provinces [17]. Lack of available health-care resources and reluctance in using face masks in early stages may be one of the reasons for non-Asian countries having higher COVID-19 mortality.

Viral load is a good indicator of treatment outcome. Wang *et al.* showed that remdesivir reduces viral load significantly in the first 10 days, but there was no significant difference compared to the placebo group [18]. However, this study was halted prematurely with incomplete recruitment due to a decline in COVID-19 infections at the time of the study, and there was insufficient power to detect assumed differences. In contrast, Beigel *et al.* showed that cumulative clinical improvement increased rapidly in the first 10 days with a decline in viral load in several categories, including "patients not receiving oxygen", "patients receiving oxygen" and "patients receiving high-flow oxygen or non-invasive mechanical ventilation" [7, 8]. The time to recovery was significantly better than the placebo group (p<0.001). Remdesivir only provides limited benefits in patients with baseline receiving ECMO at baseline as the cumulative clinical improvement was only slightly higher than the placebo group. Severe adverse events in both the treatment

group and the placebo group were comparable. Overall, the use of remdesivir did not increase the occurrence of severe adverse events. A majority of the adverse events affected the respiratory system and cardiovascular system. Termination of treatment was seen in all pooled studies due to serious adverse events [6-10, 18].

Compared with the previous meta-analysis, we included more studies to assess clinical efficacy [4]. Since the studies involved patients of different baseline ordinal score, the effects may vary across individuals. By using the random-effects model and the mortality data available in the selected studies, we have shown that reduction of mortality risk was not associated with remdesivir. Further studies are required to conclude their associations. We have also included more studies to conduct subgroup analysis within the remdesivir group, showing that the chance of recovery was significantly higher in patients without the need for invasive ventilation at baseline. Also, younger patients had double the chance of recovery compared with older populations. Good therapeutic outcome was also observed in another clinical trial involving patients with moderate COVID-19 [19]. Spinner *et al.* further showed that a 5-day course of remdesivir had a statistical significance in clinical status compared with standard care; while 10-day course did not show a similar statistical significance [19]. This may explain the earlier study conducted by Antinori *et al.* in May 2020, showing that over 60% patients (22 out of 35) had negative viral load after a median of 12 days (IQR: 9.25-16.75) of receiving the treatment of remdesivir [20].

The recent WHO Living Guideline recommends weakly against the use of remdesivir for COVID-19 patient of any severity [21]. However, there are knowledge gaps concerning uses and effects of remdesivir for specific groups, such as different severity of illness, differences in time since onset of illness, differences in age of the patients, use for pregnant woman, and duration of therapy. This meta-analysis provides further information to bridge the gaps.

## Conclusion

Remdesivir is effective in the treatment of severe COVID-19 patients of younger age and without the need of invasive ventilation. It reduces time to clinical improvement and reduces mortality. Clinical improvement of remdesivir patients is not associated with ethnicity. Severe adverse events should be carefully monitored.

## Author Contributions

Literature search was done by Zhipeng Yan and Professor Ching-Lung Lai. Study design was done by Zhipeng Yan and Dr. Ka Shing Cheung. Figures, data collection, data analysis, data interpretation and manuscript writing were done by Zhipeng Yan, Prof. Ching-Lung Lai, Eric Ho-Yin Lau and Dr. Ka Shing Cheung.

## Acknowledgement

We would like to thank Qiqi Zhang for technical assistance.

## Ethical Approval

No ethical approval is required since the whole review is based on published data on readily accessible databases.

## Consent to Participate

Not applicable.

## Consent for Publication

Not applicable.

## Availability of Data and Materials

The datasets generated during and/or analysed during the current study are available on electronic databases (PubMed, Embase, Medline, Cochrane). All data generated or analysed during this study are included in this published article and its supplementary information files.

## Competing Interests

Professor Ching-Lung Lai has given sponsored lectures on viral hepatitis for Gilead Sciences Inc. ZY, KSC and EHYL declare that they have no competing interests.

## Funding

None.

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