The Effectiveness and Safety of Remdesivir for Covid-19: A Quantitative Meta-Analysis

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INTRODUCTION

- Remdesivir is an antiviral, working by inhibiting RNA-dependent RNA polymerase (RdRp) in vitro, interfering with the virus production.[1]
- It has been shown as a promising treatment for Covid-19, an infectious disease causing acute respiratory distress syndrome
- The United States Food and Drug Administration (FDA) granted approval for remdesivir therapy among adult and pediatric Covid-19 patients (≥ 12 years and ≥40 kilograms) who require hospitalization on October 22, 2020.
- The existing evidence on the efficacy and safety of remdesivir remains inconsistent across clinical trials.
- The results from Biegel JH, 2020 study [2], a randomized control trial (RCT) confirmed the efficacy of remdesivir in mortality and clinical improvement. Three other RCTs [3-5] did not demonstrate mortality benefit or clinical improvement for the treatment of Covid-19.

OBJECTIVES

The aim of this paper was to evaluate the effectiveness (mortality and clinical improvement at day 14 and 28, discharge status, length of stay) and safety outcome (overall adverse effects at day 28) of remdesivir for Covid-19 in adults.

METHODS

Search & Study Selection

- A literature search was performed on PubMed, Cochrane, Embase, World Health Organization (WHO) global literature, clinicaltrials.gov, and medrxiv.org databases from December 2019 to June 2021. Title/abstract and full-text screening were conducted to identify relevant articles using Covidence.
- Search terms were designed to include RCTs or Observational studies (OBS) in patients with confirmed diagnosis of Covid 19,treated with remdesivir in the intervention/ exposure group and a placebo, other active therapy, or routine care/ SOC in the control/ unexposed group.

Data analysis

- We assessed the forest plots for quantitative estimates and assessed heterogeneity with Cochrane's Q test and I-squared value to identify the proportion of between-study variability. The overall pooled relative risk (RR) and 95% confidence interval (CI) were computed statistically by DerSimonian- Laird random-effects model. The Cochrane Risk of Bias (ROB) 2.0 tool and the Newcastle-Ottawa Scale (NOS) score were used for assessing the quality of the studies.

RESULTS

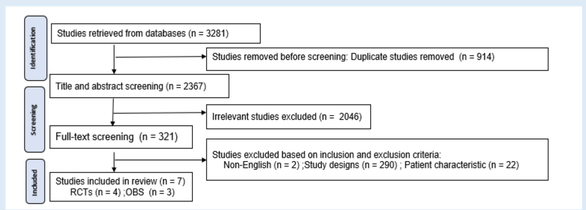

FIGURE 1. PRISMA Flow Chart

RESULTS

Study; country	Study design; single vs multicenter	Study period	Sample size	Mean age	% male	Control type	Remdesivir duration	Baseline oxygen status n (%)	Comorbidity n (%)
Biegel JH, 2020[2]; multinational	RCT; multicenter	Feb to Apr, 2020	1062	58.9	64.4	Placebo	At least 10 days	NIV/HF – 93 (18.2); MV/ECMO – 285 (26.8)	HTN – 533 (50.7) CVD – 185 (17.4) DM – 322 (30.6)
Wang Y 2020[3]; China	RCT; multicenter	Feb to Mar, 2020	237	65.0	59.3	Placebo	10 days	NIV/HF – 37 (30); MV/ECMO – 1 (0.4)	HTN – 102 (84) CVD – 17 (7.2) DM – 56 (46)
Spinner CD, 2020[4]; multinational	RCT; multicenter	Mar to Apr, 2020	584	57.0	61.1	Standard of care	5 or 10 days	NIV/HF – 5 (0.8); MV/ECMO – N/A	HTN – 248 (27.5) CVD – 329 (56.3) DM – 232 (25.8)
Pan HC, 2020[5]; multinational	RCT; multicenter	Mar, 2020	5451	N/A	62.9	Standard of care	10 days	NIV/HF – N/A; MV/ECMO – 254 (64)	HTN – N/A CVD – N/A DM – 1373 (25.2)
Flisiak R, 2020[6]; Poland	Retrospective cohort; multicenter	Mar to Aug, 2020	333	57.4	61.5	Lopinavir/ ritonavir	5 to 10 days	NIV/HF – N/A; MV/ECMO – N/A	HTN – 166 (49.8) CVD – 58 (17.4) DM – 67 (20.1)
Pasquini Z, 2020[7]; Italy	Retrospective cohort; single center	Feb to Mar, 2020	51	67.2	92.2	Standard of care	10 days	NIV/HF – N/A; MV/ECMO – 25 (49)	HTN – 28 (59.4) CVD – 11 (21.5) DM – 7 (13.7)
Kalligeros M, 2020[17]; USA	Retrospective cohort; multicenter	Feb to May, 2020	224	59.0	67.0	Supportive care	10 days	NIV/HF – 55 (24.9); MV/ECMO – 43 (19.5)	HTN – 87 (38.8) CVD – 49 (21.9) DM – 60 (26.8)

Table 1. Characteristics of the studies included in the analysis

NIV/HF – Non-invasive ventilation or high-flow oxygen, MV/ECMO – Mechanical ventilation or extracorporeal membrane oxygenation, HTN – Hypertension, CVD – Cardiovascular diseases (Ischemic heart diseases, heart failure), DM – Diabetes, N/A – Information not available, RCT – Randomized control trial

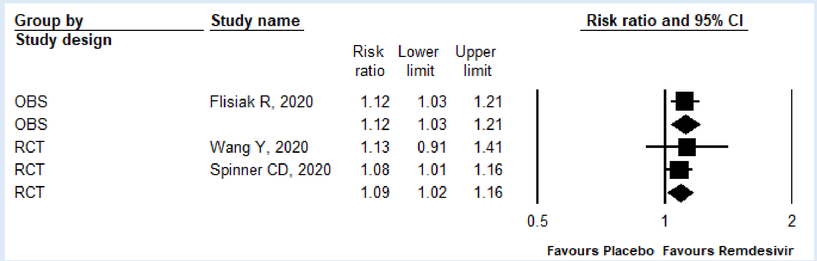

FIGURE 2. Forest plot representing the relative risk of clinical improvement comparing patients treated with remdesivir versus those in control group at Day 28(+/-1). Subgroup analysis showed an overall pooled risk ratio of 1.09 (1.02, 1.16; I^2= 0%; p -heterogeneity:0.72) for RCT and of 1.12 (1.03, 1.21 ; I^2=NA; p-heterogeneity: NA) for OBS.

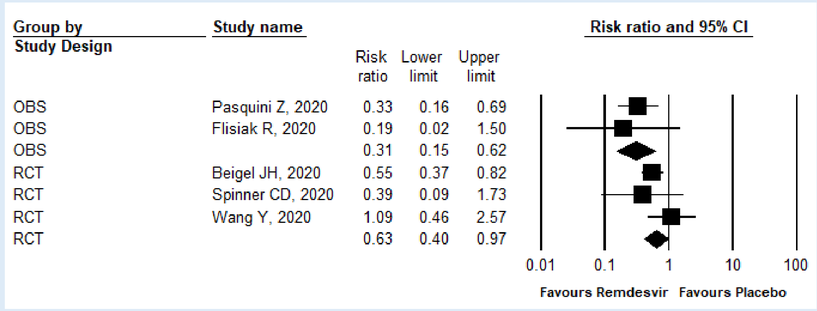

FIGURE 3. Forest plot representing the relative risk of mortality comparing patients treated with remdesivir versus those in control group at Day 15 (+/-1). Subgroup analysis by study design showed a pooled risk ratio of 0.63 (0.40, 0.97; I^2= 15.5%; p-heterogeneity=0.31) for RCT and of 0.31 (0.15, 0.62; I^2=0%; p-heterogeneity=0.63) for OBS.

RESULTS

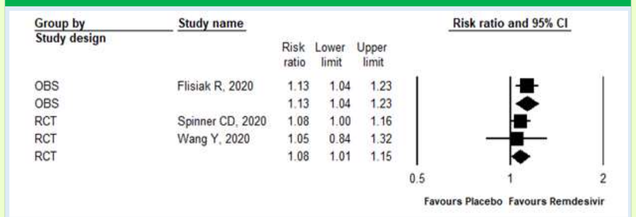

FIGURE 4. Forest plot representing the discharge rate at Day 28. Subgroup analysis showed a pooled risk ratio of 1.08 (1.01, 1.15; I^2= 0%; p-heter value=0.82) for RCT and of 1.13 (1.04, 1.23; I^2=NA; p-heter: NA) for OBS.

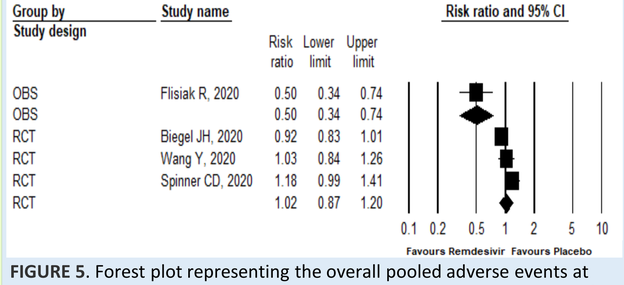

FIGURE 5. Forest plot representing the overall pooled adverse events at Day 28. Subgroup analysis showed pooled risk ratio of 1.02 (0.87, 1.20; I^2= 68.9%; p-heter: 0.04) for RCT and of 0.50 (0.34, 0.74; I^2= NA; p-heter: NA) for OBS.

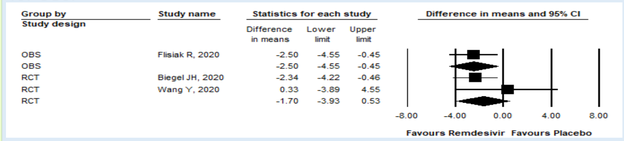

FIGURE 6. Forest plot representing the mean length of hospital stay at Day 28. Subgroup showed a mean difference of -1.70 (-3.93, 0.53); I^2= 21.9%; P value=0.25) RCT and of -2.50 (-4.55, – 0.45); I^2=NA; P value=NA) for OBS.

CONCLUSIONS

In the current meta-analyses, evidence showed effectiveness and safety in remdesivir in terms of mortality, clinical improvement, and discharge rate compared to the control group at day 28. Length of hospital stay in the remdesivir group was not different from that in the control group.

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