



# A shorter symptom onset to remdesivir treatment (SORT) interval is associated with a lower mortality in moderate-to-severe COVID-19: A real-world analysis

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## ABSTRACT

**Objectives:** Remdesivir is the current recommended anti-viral treatment in moderate-to-severe COVID-19. However, data on impact of timing of therapy, efficacy, and safety are limited. We evaluated the impact of timing of remdesivir initiation (symptom onset to remdesivir treatment [SORT] interval) on in-hospital all-cause mortality in patients with moderate-to-severe COVID-19.

**Methods:** This retrospective study was conducted between June 25 and October 3, 2020, at a tertiary care dedicated COVID center in India. Patients with moderate-to-severe COVID-19 (moderate: SpO<sub>2</sub> <94%; severe: SpO<sub>2</sub> <90%) were included. The main outcome was impact of SORT interval on in-hospital all-cause mortality. Subgroups were formed and analyzed based on SORT interval.

**Results:** Of 350 patients treated with remdesivir, 346 were included in the final analysis. Overall, 76 (22.0%) patients died (moderate: 3 [2.8%], severe: 73 [30.8%]). All-cause mortality was significantly lower in patients with SORT interval ≤9 days (n = 260) vs SORT interval >9 days (n = 86; 18.1% vs 33.7%; p = 0.004). The odds of death were significantly lower in patients with SORT interval ≤9 days vs >9 days (odds ratio = 0.43; 95% CI, 0.25–0.75; p = 0.003).

**Conclusion:** Remdesivir initiation ≤9 days from symptom onset was associated with mortality benefit, defining a treatment window and reinforcing the need for appropriately-timed remdesivir in moderate-to-severe COVID-19.

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## Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (World Health Organization, 2020a), has resulted in more than 1.18 million deaths worldwide as of October 31, 2020 (World Health Organization, 2020b).

Remdesivir, a nucleotide analog prodrug with broad antiviral activity, has demonstrated in vitro activity against SARS-CoV-2 and in vivo activity in a primate model of SARS-CoV-2 infection (Pizzorno et al., 2020; Williamson et al., 2020). Remdesivir received Emergency Use Authorization (EUA) on May 1, 2020 from the United States Food and Drug Administration (FDA) for treatment of moderate-to-severe

COVID-19 (US FDA, 2020a). On October 22, 2020, the FDA approved remdesivir as the first COVID-19 anti-viral agent in adult and pediatric patients (aged ≥12 years and weighing at least 40 kg) requiring hospitalization (US FDA, 2020b).

The efficacy and safety of remdesivir in COVID-19 have been studied in a few clinical trials (Beigel et al., 2020; Goldman et al., 2020; Spinner et al., 2020; Wang et al., 2020). Further, benefits of early initiation of remdesivir have been demonstrated in patients with COVID-19. Previous studies have shown that patients with COVID-19 treated with remdesivir (within 10 days of symptom onset) had a shorter time to recovery (Beigel et al., 2020; Wang et al., 2020) and a trend towards lower mortality compared with placebo (Wang et al., 2020). Remdesivir therapy was associated with earlier clinical improvement (18 vs 23 days) and trend towards a lower 28-day mortality (11% vs 15%) in adult patients hospitalized for severe COVID-19 treated within 10 days of symptoms compared with placebo (Wang et al., 2020). However, prior studies focused primarily on clinical recovery, with no reports so far correlating symptom onset to remdesivir treatment

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(SORT) interval (i.e. earlier vs later initiation of remdesivir) and mortality, especially in moderate-to-severe disease. Further, the recent World Health Organization (WHO)–sponsored solidarity trial results raised several questions on the efficacy of remdesivir in COVID-19 (WHO Solidarity Trial Consortium, 2021).

Inconsistent data about the efficacy of remdesivir are attributable to various factors including the heterogenous nature of COVID-19 treatment in the pandemic as treatment options evolved, lack of clarity of the optimal timing of drug initiation, treatment efficacy assessed from either ‘symptom onset’ or ‘diagnosis onset,’ and difference in ‘standard of care’ across the globe. Specifically, the relationship between timing of remdesivir initiation (from symptom onset) and outcomes has not been clearly elucidated. There is a need to evaluate the effect of optimal remdesivir initiation timing that would improve outcomes in COVID-19, especially in the subsets of moderate-to-severe disease. This study aimed to evaluate the impact of SORT interval on clinical outcomes in the subsets of moderate-to-severe COVID-19.

## Methods

### Study design

This single-center retrospective study was conducted between June 25, 2020 and October 3, 2020 at a tertiary dedicated COVID care hospital in adult patients with moderate-to-severe COVID-19 in Bangalore, India. Data on patient demographics, clinical characteristics, and outcomes were collected from health records of the hospital. Ethical approval was obtained from the Institutional Review Board of the participating site. De-identified patient data were used for analysis.

**Table 1**

Characteristics and outcomes of the overall study population<sup>a</sup> and comparison of outcomes in patients with COVID-19 with SORT interval  $\leq 9$  and  $> 9$  days.

|  | Total<br>(N = 346)     | SORT interval $\leq 9$ days<br>(n = 260) | SORT interval $> 9$ days<br>(n = 86) | p-Value <sup>b</sup> |
|--|------------------------|--|--------------------------------------|----------------------|
| Age (years), median (IQR)                          | 60 (49.3–69)           | 60 (49.8–69)                             | 59 (49.3–68)                         | 0.96                 |
| Sex, n (%)   |                        |  |                                      |                      |
| Male   | 270 (78.0)             | 202 (77.7)                               | 68 (79.1)                            | 0.91                 |
| Female   | 76 (22.0)              | 58 (22.3)                                | 18 (20.9)                            |                      |
| Comorbidities, n (%)                               |                        |  |                                      |                      |
| DM   | 173 (50.0)             | 133 (51.2)                               | 40 (46.5)                            | 0.17                 |
| HTN  | 163 (47.1)             | 119 (45.8)                               | 44 (51.2)                            |                      |
| CHD  | 54 (15.6)              | 41 (15.8)                                | 13 (15.1)                            |                      |
| CKD  | 18 (5.2)               | 9 (3.5)                                  | 9 (10.5)                             |                      |
| Chronic respiratory diseases (asthma, COPD), n (%) | 12 (3.5)               | 8 (3.1)                                  | 4 (4.7)                              |                      |
| Ancillary therapies, n (%)                         |                        |  |                                      |                      |
| Corticosteroids                                    | 346 (100.0)            | 260 (100.0)                              | 86 (100.0)                           | 0.73                 |
| Convalescent plasma                                | 131 (37.9)             | 103 (39.6)                               | 28 (32.6)                            |                      |
| Tocilizumab  | 37 (10.7)              | 28 (10.8)                                | 9 (10.5)                             |                      |
| SORT (days), median (IQR)                          | 6 (4–9)                | 5 (4–7)                                  | 11 (10–12)                           | <0.001               |
| Disease (COVID-19) severity, n (%)                 |                        |  |                                      |                      |
| Moderate   | 109 (31.5)             | 86 (33.1)                                | 23 (26.7)                            | 0.34                 |
| Severe   | 237 (68.5)             | 174 (66.9)                               | 63 (73.3)                            |                      |
| Outcomes (overall), n (%)                          |                        |  |                                      |                      |
| Discharged   | 270 (78.0)             | 213 (81.9)                               | 57 (66.3)                            | 0.004                |
| Death  | 76 (22.0)              | 47 (18.1)                                | 29 (33.7) <sup>c</sup>               |                      |
| LOHS (days), median (IQR)                          | 11 (7–16)              | 10 (7–16)                                | 12 (7–17)                            | 0.34                 |
| Mortality (disease severity), n (%)                |                        |  |                                      |                      |
| Moderate   | 3 (0.9) <sup>d</sup>   | 3 (1.2)                                  | 0 (0.0)                              | 0.28                 |
| Severe   | 73 (21.1) <sup>d</sup> | 44 (16.9)                                | 29 (33.7)                            |                      |

CHD, chronic heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; LOHS, length of hospital stay; SORT, symptom onset to remdesivir treatment.

<sup>a</sup> Of the 350 patients, four were excluded from the analysis due to drug discontinuation, and 346 were analyzed.

<sup>b</sup> p-Values correspond to the comparisons of SORT  $\leq 9$  days vs  $> 9$  days.

<sup>c</sup> Differences in mortality outcomes expressed as rate difference –15.6 (95% CI: –26.7 to –4.6).

<sup>d</sup>  $p < 0.001$  for patients with moderate vs severe disease; mortality rates presented here are with respect to the overall population and correspond to 2.8% and 30.8%, with respect to moderate and severe groups.

### Study population

Inclusion criteria were hospitalized patients with SARS-CoV-2 infection as confirmed by reverse-transcription polymerase chain reaction assay, radiologic evidence of pneumonia, and peripheral oxygen saturation (SpO<sub>2</sub>) of  $< 94\%$  (while breathing room air).

Moderate disease was defined as presence of hypoxia (SpO<sub>2</sub>  $< 94\%$ , range: 90%–94%) while breathing room air and respiratory rate  $\geq 24$  breaths per minute (Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division), 2020; World Health Organization, 2020c). Severe disease was defined as presence of clinical signs of pneumonia and one of the following criteria: SpO<sub>2</sub>  $< 90\%$  while breathing room air, respiratory rate  $> 30$  breaths per minute, heart rate  $> 120$  beats per minute, presence of acute respiratory distress syndrome (ARDS), sepsis, or septic shock (Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division), 2020; World Health Organization, 2020c).

### Treatment

Patients received intravenous remdesivir 200 mg on day 1 as loading dose, followed by a maintenance dose of 100 mg daily for a total of 5–10 days, manufactured by three different pharmaceutical companies. Patients also received other drugs as per protocol, including corticosteroids, anticoagulants, and other supportive therapy. A few patients also received other experimental therapies, including convalescent plasma, tocilizumab, and thrombolytics.

Only patients admitted to the hospital during the study period and receiving a minimum of 5 doses of remdesivir were included in the final analysis.

Outcome measures

Data on clinical and laboratory findings, including mortality, length of hospital stay (LOHS), and safety outcomes (adverse events [AEs], serious adverse events [SAEs], and suspected drug-related hypersensitivity reactions), were extracted from the medical records.

Demographic parameters analyzed included age, sex, and comorbidities (diabetes mellitus, hypertension, chronic kidney disease [CKD], chronic heart disease [CHD], and chronic respiratory diseases among others). The main outcome measure analyzed was the impact of SORT interval on in-hospital all-cause mortality. Other outcomes analyzed included in-hospital all-cause mortality, AEs, SAEs, treatment-emergent AEs, and overall LOHS.

Statistical analysis

Results were summarized descriptively as numbers and percentages, means and standard deviations, or medians and inter-quartile ranges. The difference between means of continuous variables was assessed using t-test/Mann Whitney-U test and difference between proportions of categorical variables, using Fisher’s exact test/Chi-square test.

Kaplan–Meier plots were used to determine the impact of SORT interval ( $\leq 6$  vs  $> 6$ ,  $\leq 7$  vs  $> 7$ ,  $\leq 8$  vs  $> 8$ ,  $\leq 9$  vs  $> 9$ , and  $\leq 10$  vs  $> 10$  days) on survival probability (all-cause mortality) and the differences in the sub-groups were determined using log-rank test. Odds ratio (OR) and 95% confidence interval (CI) were calculated, using Mantel Haenszel method, to compare mortality outcomes between the cohorts with the specific SORT interval derived from the Kaplan–Meier plots.

Differences in outcomes between the study groups were considered significant if  $p < 0.05$  (two-sided). All statistical calculations were performed using R software (R 4.0.2).

Results

A total of 350 patients with moderate-to-severe COVID-19 infection received remdesivir, of which 346 were included for the final analysis (four patients were excluded due to SAEs leading to drug discontinuation). The median (range) age was 60 (24–94) years, with the majority being male ( $n = 270$ ; 78.0%; Table 1). Among the hospitalized patients, one-third had moderate disease ( $n = 109$ ; 31.5%), and 237 (68.5%) had severe disease. Fifty patients (14.5%) required mechanical ventilation. Most patients had  $\geq 1$  comorbidity ( $n = 243$ ; 70.2%), including diabetes mellitus ( $n = 173$ ; 50.0%), hypertension ( $n = 163$ ; 47.1%), CHD ( $n = 54$ ; 15.6%), CKD ( $n = 18$ ; 5.2%), and chronic respiratory disease (asthma/chronic obstructive pulmonary disease [COPD];  $n = 12$ ; 3.5%).

In addition to remdesivir, all patients received corticosteroids, 131 (37.9%) received convalescent plasma, and 37 (10.7%) received tocilizumab.

Of the 346 admitted patients, 270 (78.0%) were discharged, and 76 (22.0%) died. In the subset with moderate disease, 106 (97.2%) patients were discharged and three (2.8%) died. In the subset with severe disease, 164 (69.2%) patients were discharged and 73 (30.8%) died.

The median (interquartile range [IQR]) LOHS was 11 (7–16) days in the overall group, 9 (6–12) days in the subset with moderate disease, and 13 (8–18) days in the subset with severe disease.

Kaplan–Meier plots demonstrated significant difference in the probability of survival for SORT interval  $\leq 9$  vs  $> 9$  days ( $p = 0.03$ ; Figure 1; Appendix, Figure A1) but not for the other intervals. Based on this, the two subgroups of SORT interval  $\leq 9$  vs  $> 9$  days were further analyzed to evaluate the impact of the timing of remdesivir initiation on outcomes.

Table 1 shows demographic characteristics and outcomes of patients with SORT interval  $\leq 9$  vs  $> 9$  days. The demographic

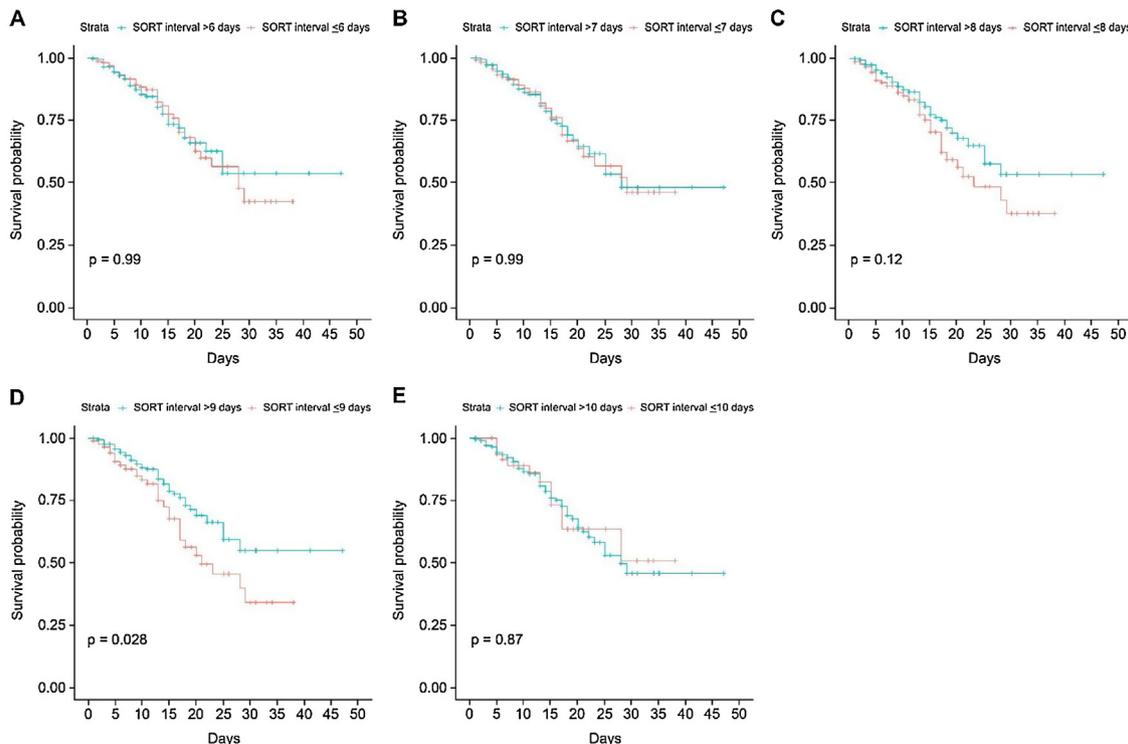


Figure 1. Kaplan–Meier curves for various SORT intervals. SORT, symptom onset to remdesivir treatment.

(age and sex) and clinical characteristics (comorbidities and severity distribution) were comparable between the two groups. Overall, 260 (75.1%) patients had a SORT interval of  $\leq 9$  days, while 86 (24.9%) had a SORT interval of  $> 9$  days. All-cause mortality was significantly lower in the former group compared with the latter group (18.1% vs 33.7%;  $p = 0.004$ ; rate difference:  $-15.6$  [95% CI,  $-26.7$  to  $-4.6$ ]). Although not statistically significant, median LOHS was numerically lower in patients with SORT interval  $\leq 9$  days compared with  $> 9$  days (10 vs 12 days;  $p = 0.34$ ).

The odds of death were significantly lower in patients with SORT interval  $\leq 9$  days compared with  $> 9$  days (OR = 0.43; 95% CI, 0.25–0.75;  $p = 0.003$ ).

AE of transaminitis was observed in 44 (12.7%) patients and acute kidney injury (AKI) in 23 (6.6%) patients. Among the 350 patients, SAEs leading to drug discontinuation were observed in four (1.1%) patients. Of these, one (0.3%) patient (moderate COVID-19) had transaminitis  $> 5$  times upper limit of normal (after three doses) and was discharged uneventfully; three (0.9%) patients had AKI (estimated glomerular filtration rate  $< 30$  mL/min after three doses in two patients and after two doses in one patient), of which two patients survived (moderate COVID-19,  $n = 1$ ; severe COVID-19,  $n = 1$ ) and one patient (severe COVID-19) died. No hypersensitivity reactions were noted.

## Discussion

This study evaluated the impact of SORT interval on in-hospital all-cause mortality, LOHS and safety outcomes in patients with moderate-to-severe COVID-19 treated with remdesivir. The majority of patients in this cohort had severe disease (68.5%) and reported  $\geq 1$  comorbidity (70.2%). Patients with SORT interval  $\leq 9$  days had lower mortality than those with SORT interval  $> 9$  days (18.1% vs 33.7%), with the difference largely driven by the severe subset. The overall all-cause mortality in this cohort was 22.0%, with mortality higher in severe disease than moderate disease (30.8% vs 2.8%). Median LOHS for all patients was 11 days, longer in severe disease than moderate disease (13 days vs 9 days).

Most global studies have studied the effects of remdesivir in COVID-19 by comparing with placebo or evaluating different durations of remdesivir treatment (Table 2). However, none of these studies evaluated mortality outcomes based on SORT interval (early vs late initiation). Clinical benefits of early treatment have been demonstrated in rhesus macaques (a primate model) infected with SARS-CoV-2 (Williamson et al., 2020). Anti-virals are maximally effective in earlier stages of the disease when there is active viral replication – defining this therapeutic window is of paramount importance. Additionally, considering that the average latency between viral exposure and clinical symptoms is 5 days,

**Table 2**  
Summary of outcomes reported in COVID-19 patients treated with remdesivir.

| Parameters                  | ACTT-final report (Beigel et al., 2020)  | Wang et al. (2020)  | Goldman et al. (2020)   | Solidarity trial (WHO Solidarity Trial Consortium, 2021) | Current study                                     |
|-----------------------------|--|---|---|--|---|
| Sample size and treatment   | N = 1062   | N = 237   | N = 397   | N = 11,266   | N = 346   |
|                             | R (n = 541) vs placebo (n = 521)   | R (n = 158) vs placebo (n = 78)   | R 5-days (n = 200) vs R 10-days (n = 197)   | R (n = 2743) vs control (n = 2708)                       |   |
| Baseline oxygen requirement |  |   |   |  |   |
| Room air                    | 75 (13.9%) vs 63 (12.1%)   | 0 (0%) vs 3 (4%)  | 34 (17%) vs 21 (11%)  | 661 (24.1%) vs 664 (24.5%)                               | NIL   |
| On supplemental oxygen      | 232 (42.9%) vs 203 (39.0%)   | 129 (82%) vs 65 (83%)   | 113 (56%) vs 107 (54%)  | 1828 (66.6%) vs 1811 (66.9%)                             | 161 (46.5%)                                       |
| On NIV/HFNC                 | 95 (17.6%) vs 98 (18.8%)   | 28 (18%) vs 9 (12%)   | 49 (24%) vs 60 (30%)  |  | 135 (39.0%)                                       |
| On MV/ECMO                  | 131 (24.2%) vs 154 (29.6%)   | 0 (0%) vs 1 (1%)  | 4 (2%) vs 9 (5%)  | 254 (9.3%) vs 233 (8.6%)                                 | 50 (14.5%)  |
| Outcomes assessed           |  |   |   |  |   |
| Time to recovery, days      | Median (95% CI): 10 (9–11) vs 15 (13–18) days  | Median (IQR): 21.0 (13.0–28.0) vs 23.0 (15.0–28.0) days   | Median (IQR): 10 (6–18) vs 11 (7–NR) days   | Not reported   | Not reported                                      |
| Mortality                   | By day 15: 6.7% vs 11.9%<br>By day 29: 11.4% vs 15.2%  | At day 28: 14% vs 13%   | Day 14: 8% vs 11%   | At day 28: 12.5% vs 12.7%                                | Overall: 22.0%<br>Moderate: 2.8%<br>Severe: 30.8% |
| LOHS, median days           | Initial <sup>a</sup> median (IQR): 12 (6–28) vs 17 (8–28)  | Median (IQR): 25.0 (16.0–38.0) vs 24.0 (18.0–36.0)  | Median (IQR) among patients discharged on/ before day 14: 7 (6–10) vs 8 (5–10)        | Not reported   | 11 (7–16)   |
| Outcomes based on SORT      |  |   |   |  |   |
| SORT <sup>b</sup> , days    | Median (IQR): 9 (6–12) vs 9 (7–13)   | Median (IQR): 11 (9–12) vs 10 (9–12)  | Median (IQR): 8 (5–11) vs 9 (6–12) days   | Not reported   | Median (IQR): 6 days (4–9)                        |
| SORT <sup>b</sup> , groups  | $\leq 10$ days and $> 10$ days   | $\leq 10$ days and $> 10$ days  | $< 10$ days and $\geq 10$ days  | Not reported   | $\leq 9$ days and $> 9$ days                      |
| Clinical improvement        | Median time to recovery (R vs placebo)<br>$\leq 10$ days: 9 vs 15 (rate ratio for recovery = 1.37) | Median (IQR) time (R vs placebo)<br>$\leq 10$ days: 18.0 (12.0–28.0) vs 23.0 (15.0–28.0); hazard ratio = 1.52 (95% CI: 0.95–2.43) | Discharge rate in the overall population<br>$< 10$ vs $\geq 10$ days SORT: 62% vs 49% | Not reported   | Not reported                                      |
| All-cause mortality         | Not reported   | $\leq 10$ days: 11% vs 15%; $> 10$ days: 14% vs 10%, at day 28  | Not reported  | Not reported   | 18.1% vs 33.7%                                    |
| LOHS, days                  | Not reported   | Not reported  | Not reported  | Not reported   | 10 (7–16) vs 12 (7–17)                            |

ACTT, Adaptive Covid-19 Treatment Trial; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HFNC, high flow nasal cannula; IQR, interquartile range; LOHS, length of hospital stay; MV, mechanical ventilation; NIV, non-invasive ventilation; NR, not reported/possible to estimate; R, remdesivir; SORT, symptom onset to remdesivir treatment.

<sup>a</sup> Readmission: 5% vs 3%.

<sup>b</sup> SORT: in non-remdesivir group, it refers to time between symptom onset and receiving either placebo or non-remdesivir treatment.

minimizing the interval between symptom onset and treatment initiation is critical from an outcomes perspective. Our subgroup analysis showed that patients with SORT interval  $\leq 9$  days had a significantly lower all-cause mortality than those with SORT interval  $> 9$  days (18.1% vs 33.7%;  $p = 0.004$ ). The corresponding OR was 0.43 (95% CI, 0.25–0.75;  $p = 0.003$ ), suggesting a survival benefit of earlier remdesivir treatment in moderate-to-severe disease. In the Adaptive Covid-19 Treatment Trial (ACTT-1), the rate ratio for clinical recovery (remdesivir vs placebo) was 1.37 (95% CI, 1.14–1.64) in those who received remdesivir within 10 days of symptom onset and 1.20 (95% CI, 0.94–1.52) in those who received remdesivir after 10 days; however, there was no mortality benefit mentioned (Beigel et al., 2020). Similarly, in the study by Wang et al, the 28-day mortality was lower in patients treated with remdesivir compared to placebo within 10 days of symptom onset (11% vs 15%; difference  $-3.6\%$  [95% CI,  $-16.2$  to  $8.9$ ]) (Wang et al., 2020). However, no comparison was made between early and late treatment among remdesivir-treated patients. In the study by Goldman et al., in patients not requiring mechanical ventilation, hospital discharge rate was higher in patients who had symptoms for  $< 10$  days before receiving the first dose of remdesivir, than those who had symptoms for  $\geq 10$  days (62% vs 49%) (Goldman et al., 2020). However, mortality with respect to SORT interval was not reported.

The more recent WHO Solidarity trial included a large number of patients on remdesivir ( $n = 2743$ ), but did not analyze outcomes based on SORT interval (WHO Solidarity Trial Consortium, 2021).

The cardinal difference between our study and other robust trials is the mortality benefit observed in our study with earlier initiation of the drug (SORT interval  $\leq 9$  days) in moderate-to-severe COVID-19. Although previous studies have considered 8 to 11 days as the median time from symptom onset to treatment for analyzing various outcomes (Beigel et al., 2020; Goldman et al., 2020; Wang et al., 2020), our study provides an objective cut-off of 9 days for mortality benefit defining the “SORT window.” Our findings also reiterate the need to consider “symptom onset” and not “date of diagnosis” as the target for intervention.

The mortality and recovery time/discharge rates reported in the published studies vary widely based on factors such as patient selection, disease severity (defined differently in various studies), treatment duration, and stage of the pandemic (with different therapeutic regimens). In our study, the mortality rate (22.0%) was higher than reported in other studies that included patients treated with remdesivir: ACTT-1 trial (overall mortality: 6.7% at day 15; 11.4% at day 29) (Beigel et al., 2020), study by Wang et al (overall mortality: 14% at day 28) (Wang et al., 2020), study by Goldman et al (overall mortality at day 14: 8% in 5-day and 11% in 10-day remdesivir treatment group respectively) (Goldman et al., 2020), and the Solidarity trial (overall mortality at day 28: 12.5%) (WHO Solidarity Trial Consortium, 2021). The higher mortality rate in our study can be explained by a greater severity of illness, as we only included patients with moderate-to-severe COVID-19. The severity of illness is evident in that all the patients in our study required supplemental oxygen, as compared to the fact that 13.9% of patients on remdesivir in the ACTT-1 and 24.1% in the Solidarity trial did not receive supplemental oxygen (Beigel et al., 2020; WHO Solidarity Trial Consortium, 2021).

In the present study, overall median (IQR) LOHS was 11 (7–16) days (moderate disease: 9 [6–12] days; severe disease: 13 [8–18] days). Median LOHS in patients with severe disease in our study was substantially lower than in Wang et al (median [IQR]: 25.0 [16.0–38.0] days) (Wang et al., 2020). However, comparison between the two studies is limited because of the differences in study design (retrospective vs randomized control trial [RCT]) and

local country protocols for discharge at that time in the pandemic, which may have impacted the duration of hospitalization.

In our study, the rate of AKI was lower than that reported by Antinori et al. (6.6% vs 22.8%) (Antinori et al., 2020). Similarly, the rate of transaminitis (12.7%) was lower than that reported by Spinner et al (alanine aminotransferase increase: 32%–34%; aspartate aminotransferase increase: 32%) (Spinner et al., 2020). SAEs leading to drug discontinuation were observed in four out of 350 patients (three [0.9%] due to AKI and one [0.3%] due to transaminitis).

Studies on several aspects of COVID-19 therapeutics, due to rapidly evolving data, have been confounded by varying treatment protocols that can have a substantial impact on the outcomes. For example, steroids in moderate doses are being uniformly used only after July 2020, when results of the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial were released (RECOVERY Collaborative Group et al., 2021). Trials without steroids or a mixed population with/without steroids, would likely report different outcomes compared to studies with uniform steroid use. Additionally, in the earlier part of the pandemic, detailed data collection and reporting were challenging as healthcare systems faced an unprecedented burden. Our study reflects real-world practice in the latter part of the pandemic, including uniform use of remdesivir and steroids and a well-prepared healthcare system. The importance of early remdesivir initiation (SORT interval  $\leq 9$  days) in our study, with a clear mortality benefit indicates an impact of the medication over and above steroids and ancillary therapies in moderate-to-severe COVID-19.

Our study has some limitations, such as the retrospective nature of the study and the lack of a control group. However, the main outcome measure was the impact of SORT interval  $\leq 9$  days and  $> 9$  days, with all patients receiving remdesivir. Additionally, with an FDA EUA for remdesivir for moderate-to-severe COVID-19 at the time of the study, it was not ethically possible to conduct an RCT with a placebo group in this subset of patients with moderate-to-severe COVID-19. Further, our study did not evaluate the optimal duration of remdesivir treatment. It is difficult to delineate the effect of remdesivir from other COVID-19-recommended medications such as steroids, as this is one of the first studies to report uniform use of both these agents. However, the observation that overall mortality was higher with SORT interval  $> 9$  days, which is the period in the disease course that steroids are known to be maximally useful (RECOVERY Collaborative Group, 2020), suggests that the mortality benefit of SORT interval  $\leq 9$  days can be attributed to remdesivir. Additionally, we used remdesivir preparations from three different companies as the demand increased exponentially.

## Conclusions

In summary, our study is one of the first to show that in the subset of hospitalized patients with moderate-to-severe COVID-19, SORT interval  $\leq 9$  days is associated with a mortality benefit. Our findings reinforce the need to consider earlier remdesivir initiation from symptom onset in moderate-to-severe COVID-19 infection.

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**Declaration of interests**

The authors do not have any competing interests to declare.

**Ethical approval**

Office of Institutional Ethics Committee–Bio Medical Research, Apollo Hospitals, Bangalore, after due ethical and scientific consideration, has approved the study. Application number: AHB-BMR-006/09-20.

**Contributors**

All authors contributed to study design, data collection, and interpretation. All authors critically reviewed and approved the final manuscript for publication. All authors had full access to the complete study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Data sharing statement**

The de-identified data that support the findings of this study are available from the corresponding author (RMM) upon reasonable request.

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**Appendix A**

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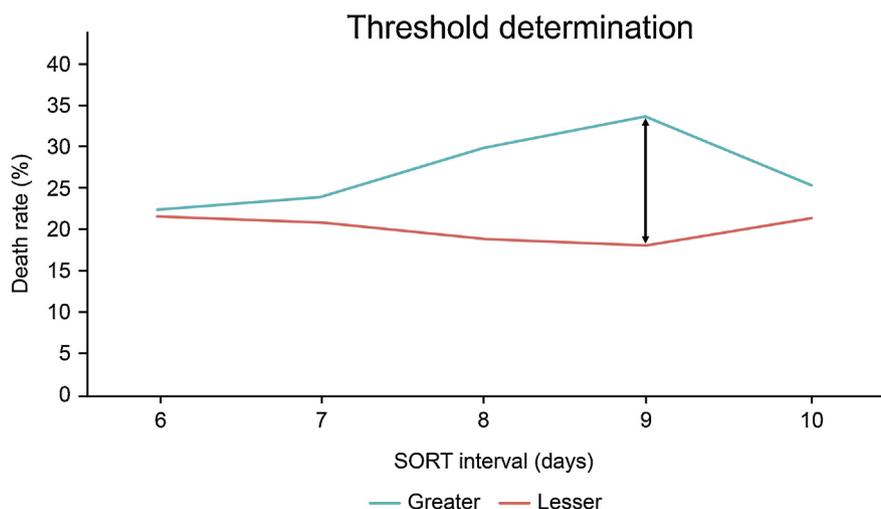
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**Figure A1.** Mortality rate curve for threshold determination. SORT, symptom onset to remdesivir treatment.

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