

Effect of Remdesivir Administration on Occurrence of Major Adverse Cardiac Events in Critically Ill COVID-19 Pneumonia: A Retrospective Observational Study

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ABSTRACT

Background and objectives: Major adverse cardiac events (MACE) are frequent in coronavirus disease-2019 (COVID-19). Remdesivir is used worldwide for treatment in COVID-19. In this retrospective observational study, our primary objective was to assess the impact of remdesivir administration on the incidence of MACE and associated 28 day survival in critically ill patients admitted for moderate to severe COVID-19 pneumonia.

Patients and method: We analyzed the data of 437 patients admitted in intensive care unit (ICU) and divided them into two groups: R Group (received remdesivir at ICU admission) and NR group (non-remdesivir) or based on the occurrence of MACE in ICU. We followed the data until discharge, death, or 28 days postadmission. Our primary objective was to investigate the log-odds of survival with remdesivir administration and a correlation/regression analysis of MACE with remdesivir administration in all included patients.

Result: The incidence of MACE was 72 among 437 patients, with 17 (9.3%) patients in R group vs 55 (21.8%) in NR group ($p < 0.001$). On performing correlation analysis between MACE and remdesivir administration, significant correlation coefficient of -0.168 ($p = 0.004$) was obtained. On regression analysis, the odds ratio for occurrence of MACE with remdesivir administration was 0.362 (regression coefficient: -1.014 , $p < 0.001$). It indicates a 64% decrease in the log-odds of MACE and a 16% increase in the log-odds of survival with remdesivir administration. All 72 patients with MACE had expired, suggesting a high mortality risk with cardiac complications. The odds ratio for mortality due to MACE with remdesivir administration was 0.216 (regression coefficient: -1.530 , $p < 0.001$). It indicates a 79% decrease in the log-odds of death due to MACE with remdesivir administration.

Conclusion: Our study showed significant reduction in major adverse cardiac events and mortality benefit in patients who received remdesivir in comparison to standard treatment.

Keywords: COVID-19, Intensive care, Major adverse cardiac effect, Mortality, Remdesivir.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-24189

INTRODUCTION

The symptomology of coronavirus disease-2019 (COVID-19) predominately involves respiratory system, although cardiac complications are quite common in critically ill patients. The reported incidence of cardiac injury among hospitalized COVID-19 patients is as high as 44%, with a high risk of mortality.¹⁻⁵ The common cardiac events include arrhythmia, conduction defect, myocardial infarction, heart failure, pulmonary embolism, and sudden cardiac death.⁵ The underlying pathophysiology involves the synergistic effect of local vascular inflammation on the arterial plaque and systemic inflammatory response, myocarditis due to infiltration of myocardium by mononuclear cells or by SARS-CoV-2 virus.⁶

Among antivirals, remdesivir was granted Emergency Use Authorization by the US Food and Drug Administration in May 2020 for patients hospitalized with severe COVID-19.⁷ Remdesivir requires metabolism by the host cell to convert into active form as it is adenosine prodrug analogue with broad-spectrum antiviral activity against RNA viruses. It halts RNA synthesis and viral replication by interfering with viral RNA-dependent RNA polymerase enzyme. Previous studies have suggested that prophylactic remdesivir treatment may inhibit SARS-CoV-2 replication, which might help

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How to cite this article: Panda R, Singh P, Jain G, Saigal S, Karna ST, Anand A, et al. Effect of Remdesivir Administration on Occurrence of Major Adverse Cardiac Events in Critically Ill COVID-19 Pneumonia: A Retrospective Observational Study. *Indian J Crit Care Med* 2021; <https://www.ijccm.org/doi/IJCCM/pdf/10.5005/jp-journals-10071-24189>.

Source of support: Nil

Conflict of interest: None

in minimizing the clinical symptoms by reducing pulmonary involvement.⁸⁻¹⁰ Despite an appreciable reduction in viral load, its role in reducing major adverse cardiac events (MACE) and subsequent mortality remains unclear. Thus, in a retrospective observational cohort design, our primary objective was to assess the impact of remdesivir administration on the incidence of MACE

and 28 day survival in critically ill patients admitted for moderate to severe COVID-19 pneumonia.

METHODOLOGY

This is a retrospective observational cohort study in which we have analyzed the data of patients, of either sex, admitted in intensive care unit (ICU) of our tertiary care institute from June 15 to November 30, 2020, diagnosed with moderate–severe COVID-19 pneumonia. Ethical clearance was obtained from Institutional Human Ethics Committee (IHEC-LOP/2020/IM0278) with waiver of consent as the data were anonymized. The COVID-19 confirmation was performed with a real-time reverse-transcription polymerase chain reaction assay of nasal/pharyngeal swab specimen. The criteria for ICU admission included the presence of tachypnea (respiratory rate greater than 30/minute) and SpO₂ <90% on room air, with or without hemodynamic instability. We excluded those with pregnancy, lactation, recent hospitalization (past 3 months), immunocompromised status, posttransplant, or malignancy. We divided the included patients into groups R Group (those who received injection remdesivir at ICU admission) and NR group (those who did not receive remdesivir due to lack of availability) or based on the occurrence of MACE in ICU. Injection remdesivir 100 mg was started on the day of admission in ICU, in patients who were sicker with FiO₂ requirement more than 50% and/or on ventilatory support. This criterion was followed due to limited availability of drug in the Institute. Total of six doses was administered, of which two doses were given on day one followed by once-daily therapy for 4 days. Patients with history of chronic kidney disease were not given remdesivir due to its nephrotoxic potential. We followed their data until discharge or death or 28 days since admission, which occurred first, through hospital records.

The data were collected from the manual and electronic medical records, progress charts, and nursing notes of included patients. It included demographic characteristics, comorbidities, time from onset of symptoms to ICU admission, length of ICU and hospital stay, oxygen requirement at the time of ICU admission, adult respiratory distress syndrome (ARDS) category, need for mechanical ventilation/vasopressor therapy, the occurrence of MACE, and mortality. We defined MACE as positivity of cardiac biomarker (Troponin-T) along with one or more of the following events:

- Dysrhythmias:
 - Sinus/supraventricular/ventricular arrhythmia: bradycardia (heart rate <60 beats/minute) and tachycardia (heart rate >100 beats/minute) with associated hypotension (systolic blood pressure <90 mm Hg), atrial flutter/fibrillation, paroxysmal supraventricular tachycardia, ventricular fibrillation, monomorphic/polymorphic ventricular tachycardia.
 - Atrioventricular block: Types I, II, and III.
- Myocardial infarction ± cardiogenic shock: Electrocardiographic changes or echocardiographic evidence of regional wall motion abnormality or low ejection fraction.
- Heart failure: Clinical signs of acute heart failure with transthoracic echocardiography evidence of systolic or diastolic dysfunction and elevated NT-pro BNP.
- Pulmonary embolism: Echocardiographic evidence of right ventricular dysfunction and pulmonary hypertension with hemodynamic instability.
- Cardiovascular death.

The primary objective was to investigate the 28 day survival with remdesivir administration and a correlation/regression analysis of MACE with remdesivir administration in all included patients. The secondary objective was to estimate the validity profile of time duration from onset of illness to ICU admission in relation to overall mortality and mortality due to MACE (correlation/regression analysis of mortality due to MACE with remdesivir administration) and to compare baseline demographics, ICU comorbidities (acute kidney disease, sepsis) and outcome parameters (length of ICU and hospital stay, duration of invasive ventilation, and requirement of vasopressor therapy) with regard to remdesivir administration and MACE occurrence in all included patients.

The sample size was based on convenience sampling and included all eligible patients admitted to the institution during the study period. Statistical analysis was performed using MedCalc statistical software version 19.0.7 (Acaciaaan, Belgium). The results were presented as descriptive statistics, summarized as mean (SD) or number (percentage). Data were analyzed by logistic regression, receiver operator characteristic (ROC) curve, and Youden index to calculate the diagnostic validity profile of the outcome variables. The continuous variables were compared by unpaired student *t*-test. The categorical variables were compared by Chi-square test/Fisher's exact test. A *p* <0.05 was considered significant.

RESULTS

We analyzed a total of 437 patients meeting the study inclusion and exclusion criteria in the study period (Flowchart 1). Of these, 182 received injection remdesivir (200 mg on day one followed by 100 mg for 4 days) (R Group), while 252 belonged to the NR group. The demographic characteristics and comorbidities were comparable between the groups, with most patients falling in the 45–65 age-group with mean age of 56.6 years. The most common comorbidities were hypertension, diabetes mellitus, coronary artery disease, hypothyroidism, and obesity, with a significantly higher proportion of chronic kidney disease and chronic obstructive pulmonary disease in the NR group. Most patients belonged to ARDS category 2, with a significant difference between the groups. Patients who were administered remdesivir had significantly baseline higher sequential organ failure assessment score (SOFA) score on admission (R and NR group 7.35 ± 3.78 and 6.42 ± 3.43 respectively, *p* = 0.009), suggesting more severe disease. The time from onset of illness to ICU admission, FiO₂ requirement at ICU admission, time from ICU admission to the development of cardiac event, vasopressor requirement, and the incidence of acute kidney injury during ICU stay did not differ between the groups. However, the need for invasive mechanical ventilation was higher in R group and that for noninvasive ventilation in NR group. The length of ICU/hospital stay was also higher in R group. Although the all-cause mortality rate was similar in both the groups, NR group had more MACE and associated mortality as compared to R group (Table 1).

The mean duration of illness onset to ICU admission was 5.91 vs 5.41 days in R and NR groups, respectively. The ROC analysis for time duration from illness onset to ICU admission with subsequent mortality showed no definitive association at an optimum criterion of >8 days (sensitivity 23.63%, specificity 85.49%, Youden index 0.09) with an AUC of 0.547 (95% CI: 0.499–0.595, *p* = 0.0917) (Fig. 1). The overall incidence of MACE was 72 among 437 patients, with 17 (9.3%) patients in R group vs 55 (21.8%) in NR group

Flowchart 1: Chart showing selection of the patients for retrospective study

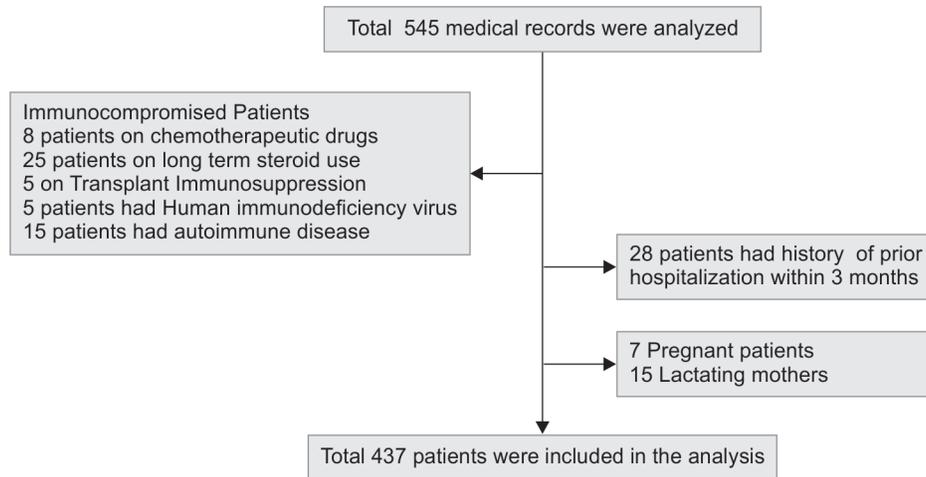


Table 1: Comparison of baseline and outcome parameters among the remdesivir and non-remdesivir groups (n = 437)

Particulars	R group (n = 182)	NR group (n = 252)	p value
Age	56.60 ± 12.40	57.70 ± 14.30	0.059
Gender (male)	133 (73)	180 (71.4)	0.990
Comorbidities			
Diabetes mellitus	87 (47.8)	134 (53.1)	0.210
Hypertension	97 (53.3)	136 (54)	0.772
Coronary artery disease	32 (17.6)	27 (10.7)	0.049
Chronic kidney disease	3 (1.6)	26 (10.3)	<0.001
COPD	0 (0)	8 (3.2)	0.023
Hypothyroidism	18 (10)	19 (7.5)	0.487
Obesity	5 (2.7)	11 (4.4)	0.445
Smoking	13 (7.1)	6 (2.4)	0.030
ARDS Category			
Category 1	25 (13.7)	64 (25.4)	0.006
Category 2	112 (61.5)	140 (55.5)	
Category 3	48 (26.4)	48 (19)	
Baseline SOFA score	7.35 ± 3.78	6.42 ± 3.43	0.009
Vasopressor therapy	72 (39.5)	72 (28.6)	0.024
Acute kidney injury	42 (23.1)	64 (25.4)	0.573
Noninvasive ventilation	76 (41.7)	148 (58.7)	<0.001
Invasive ventilation	109 (60)	104 (41.3)	<0.001
MACE	17 (9.3)	55 (21.8)	<0.001
Death	81 (44.5)	101 (40.1)	0.492
Time from onset of illness to ICU admission (days)	5.91 ± 3.50	5.41 ± 3.77	0.157
ICU LOS (days)	10.13 ± 7.48	6.58 ± 5.01	0.001
Hospital LOS (days)	14.13 ± 8.64	11.29 ± 8.64	0.001
FiO ₂ on ICU admission (%)	0.60 ± 0.44	0.51 ± 0.196	0.263
Duration of MV (days)	4.63 ± 6.00	1.80 ± 3.10	<0.001
Time from ICU admission to cardiac event (days)	14.20 ± 6.53	7.39 ± 6.92	0.973

Data presented as number (%) or mean ± standard deviation, MACE, major cardiac adverse events; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; ARDS, adult respiratory distress syndrome; SOFA, sequential organ failure assessment; LOS, length of stay. A p value <0.05 considered significant

(p <0.001). On performing correlation analysis between MACE and remdesivir administration, we observed a significant correlation coefficient of -0.168 (p = 0.004) with a likelihood ratio of 13.10. On

regression analysis, the odds ratio for occurrence of MACE with remdesivir administration was 0.362 (regression coefficient: -1.014, p <0.001). It indicates a 64% decrease in the log-odds of MACE with

remdesivir administration (Table 2). On categorizing type of MACE, the most common cardiac complication was atrioventricular block (59.7%), atrial fibrillation (11.1%), and sudden cardiac death (11.1%) (Table 3). Comparing demographic profile and comorbidities between those with MACE and without MACE, patients with MACE had a higher incidence of comorbidities, though a significant

difference was observed with CKD ($p = 0.038$) and hypertension ($p = 0.028$) only. The time from onset of illness to ICU admission, the severity of ARDS, vasopressor requirement, and incidence of acute kidney injury were also significantly higher in patients with MACE.

A total of 182 patients died among 437 patients, with 81 (44.5%) patients in R group vs 101 (40.1%) in NR group ($p = 0.492$). On regression analysis, the odds ratio for survival with remdesivir administration was 1.164 (regression coefficient: 0.152), though statistically insignificant ($p = 0.438$). It indicates a 16% increase in the log-odds of survival with remdesivir administration. Out of 182 deaths in both the groups, all 72 patients with MACE had expired, suggesting a high mortality risk with cardiac complications. The odds ratio for mortality due to MACE with remdesivir administration was 0.216 (regression coefficient: -1.530 , $p < 0.001$). It indicates a 79% decrease in the log-odds of MACE with remdesivir administration. The ROC curve analysis also showed a moderate association between remdesivir administration and MACE-related deaths (AUC 0.676) at an odds ratio of 0.216 (CI: 0.109–0.426) and correlation coefficient of -0.34 (-0.467 to -0.207 , CI: $p < 0.001$) (Table 4).

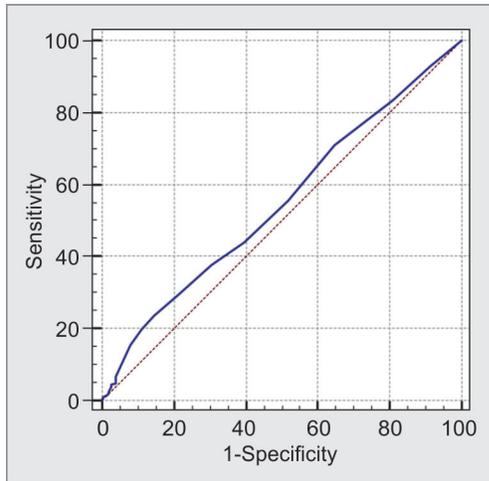


Fig. 1: ROC curve showing sensitivity and specificity of time of onset of illness to ICU admission in predicting mortality

DISCUSSION

This is a first cohort study to analyze the impact of remdesivir administration on incidence of major cardiac adverse events and their associated mortality along with all-cause mortality occurring in critically ill COVID-19 patients. Cardiovascular involvement during the infection may be caused due to direct virus toxicity or due to

Table 2: Comparison of baseline and outcome parameters in patients with and without major adverse cardiac event

Particulars	MACE (n = 72)	No MACE (n = 365)	p value
Age	61.57 ± 15.24	56.45 ± 13.05	0.204
Gender (male)	55 (76.4)	258 (70.7)	0.391
Comorbidities			
Diabetes mellitus	44 (61.1)	177 (48.5)	0.054
Hypertension	47 (65.3)	186 (51)	0.028
Coronary artery disease	11 (15.3)	48 (13.1)	0.577
Chronic kidney disease	9 (12.5)	20 (5.5)	0.038
COPD	1 (1.38)	7 (1.9)	1.00
Hypothyroidism	7 (9.7)	30 (8.2)	0.646
Obesity	3 (4.16)	13 (3.5)	0.735
Smoking	3 (4.16)	16 (4.4)	1.00
ARDS category			
Category 1	6 (8.3)	83 (22.7)	0.007
Category 2	45 (62.5)	207 (56.7)	
Category 3	21 (21.9)	75 (20.5)	
Vasopressor therapy	57 (79.2)	87 (23.8)	0.0001
Acute kidney injury	40 (55.5)	66 (18.1)	0.0001
Death	72 (100)	110 (30.1)	0.0001
Time from onset of illness to ICU admission (days)	6.24 ± 4.555	5.50 ± 3.456	0.018
ICU LOS (days)	8.79 ± 6.478	7.94 ± 6.411	0.430
Hospital LOS (days)	10.88 ± 7.667	12.81 ± 7.397	0.534
FiO ₂ on ICU admission (%)	0.6192 ± 0.21	0.5395 ± 0.34	0.941
Duration of MV (days)	4.64 ± 4.342	2.68 ± 4.788	0.229
Time from ICU admission to cardiac event (days)	8.87 ± 7.288	—	—

Data presented as number (%) or mean ± standard deviation. MACE, major cardiac adverse events; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; ARDS, adult respiratory distress syndrome; LOS, length of stay. A p value <0.05 considered significant

Table 3: Frequency of MACE events

Type of MACE (n = 73)	N (%)
Atrioventricular block	44 (61.1)
Atrial fibrillation	8 (11.1)
Heart failure	5 (6.9)
Myocardial infarction	3 (4.2)
Pulmonary embolism	1 (1.4)
Bradycardia	3 (4.2)
Sudden cardiac death	8 (11.1)

Data presented as number (%), MACE, major cardiac adverse events. A *p* value <0.05 considered significant

Table 4: Regression analysis of remdesivir administration to various outcome parameters

Particulars	Regression coefficient	Odds ratio (95% CI)	<i>p</i> value
Remdesivir administration to MACE	-1.014	0.362 (0.202–0.648)	<0.001
Remdesivir administration to survival	0.152	1.164 (0.793–1.710)	0.438
Remdesivir administration to death due to MACE	-1.530	0.216 (0.109–0.426)	<0.001

MACE, major cardiac adverse events; CI, confidence interval. A *p* value <0.05 considered significant

dysregulation of the inflammatory or immunological processes leading to a cytokine storm. It is considered that virally induced thrombi may result in acute coronary syndromes because of myocardial demand–supply mismatch resulting from tachycardia, hypotension, and hypoxemia; microvascular damage caused by diffuse microembolism; and cardiotoxicity due to inflammation-induced systemic cytokine storm.^{11,12} Chen et al. revealed that pericytes with high expression of ACE2 act as the target cardiac cell of SARS-CoV-2. Virus infection causes pericyte injury which may result in capillary endothelial cells dysfunction, inducing microvascular dysfunction.⁶ In most studies, MACE is defined as acute cardiac injury, heart failure, thromboembolic complications, atrial and ventricular arrhythmias with hemodynamic instability, and sudden cardiac death.¹³ Remdesivir has inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2 *in vitro* and in animal models.^{8,9} SARS-CoV-2 replication is also actively inhibited by remdesivir in human nasal and bronchial airway epithelial cells.¹⁰

Among demographic parameters, significant difference was seen only in the distribution of chronic kidney disease (*p* <0.001) with more patients in nonremdesivir group. This occurred mainly because we did not administer remdesivir in patients with chronic kidney disease in view of its high nephrotoxic potential.

The patients who developed cardiac complications were older (61.57 ± 15.248), of male gender (*p* = 0.391), and had high incidence of comorbidities like diabetes (*p* = 0.05) and hypertension (*p* = 0.028). Previous studies have also reported higher preponderance of cardiac complications in male gender and in patients with diabetes and hypertension.^{14–16} Thus, we identified comorbidities like hypertension, diabetes mellitus, and chronic kidney disease as risk factors for the occurrence of MACE.

In our study, the incidence of preexisting cardiovascular disease (CVD) is 13.5%, which is similar to results obtained by various

studies, where the incidence of preexisting cardiac disease in COVID-19 patients is 14–40%.^{1,2,4,17} It has also been reported that preexisting CVD is associated with high risk of MACE and poor prognosis,^{1,8,14,15,17,18} but we did not get significant association of MACE with preexisting CVD in COVID patients (*p* = 0.577). A large study among 3,011 hospitalized patients with COVID-19 showed that history of CVD is minimally associated with occurrence of cardiac adverse effects during hospital admission.⁵

In this study, we found that the most common dysrhythmia was atrioventricular block, followed by atrial fibrillation. COVID-CAPACITY is an international registry of cardiac complications in COVID patients which have reported similar incidence of cardiac complications (11.6%) in patients admitted in ICU and atrial fibrillation (4.7%) as most common cardiac event.⁵

In the remdesivir group, we observed significantly lower incidence of MACE (16.5%) than in the nonremdesivir group (76.4%). Our study has shown that there is 79% reduction in the occurrence of MACE after remdesivir administration. This is in contrast to National Institute of Allergy and Infectious Diseases funded ACTT-1 trial where arrhythmias occurred more frequently with the use of remdesivir than with placebo (8 vs 2%).¹⁹

The percentage of all-cause mortality in our study was 41.6% with no significant difference between remdesivir (44.5%) and nonremdesivir (55.5%) group. This could be explained by the fact that most patients who received remdesivir had significantly higher SOFA score at the time of ICU admission and thus were sicker as compared to nonremdesivir group. Thus, despite decrease in mortality due to MACE in remdesivir group, all-cause mortality was similar in both the groups. The ACTT-1 trial of 1,062 patients concluded that the mortality rate was 6.7% and 11.4% with remdesivir and 11.9% and 15.2% with placebo by day 15 and 29, respectively (hazard ratio, 0.73; 95% CI, 0.52–1.03).¹⁹ On comparing our results with ACTT-1 trial, we found that although the mortality was lesser in remdesivir group as compared to nonremdesivir group, the percentage of overall mortality was higher in our study. High mortality rate could be attributed due to the fact that we have included only critically ill patients admitted in ICU. Another study of 52 critically ill patients with COVID-19 in China observed the mortality rate was 61.5% by 28 days, which is quite comparable to our study.²⁰

The total number of MACE events was 72 in our cohort, of which none survived indicating high risk of mortality in this group of patients. Interestingly, there is a significantly lesser risk of mortality due to MACE in remdesivir group (38.4%) compared to nonremdesivir group (61.5%) (*p* <0.0001). On regression analysis, there is a 16% increase in chances of survival in remdesivir group. Our results showed moderately negative association between remdesivir administration and death due to MACE. This is in contrast with a study done by Toufchai et al., where 302 cardiac effects occurred with remdesivir prescribed in COVID-19 patients, among 2,603 adverse effects reports. Most of the 94 reports were serious (75, 80%), and 16 reports (17%) resulted in death.²¹

The requirement of vasopressor therapy was significantly higher in patients who had developed cardiovascular complications (*p* <0.0001) and in nonremdesivir group (*p* = 0.03). The increased requirement of vasopressor therapy in nonremdesivir group can be attributed to higher incidence of MACE in nonremdesivir group as compared to remdesivir group, in addition to other causes like sepsis and multiorgan failure.

The mean time of onset of symptoms to ICU admission was 5.91 ± 3.50 days in remdesivir group which was similar to

nonremdesivir group (5.41 ± 3.77 , $p = 0.157$), but this duration was significantly more in the patients who had developed cardiac complications (6.24 ± 4.555) as compared to patients who did not (5.50 ± 3.456 , $p = 0.018$). This result signifies that more is the duration of illness at the time of remdesivir administration, lesser will be the benefit in terms of mitigating cardiac complications. The average duration between ICU admission to cardiac event was 8.87 ± 7.288 days and was more in remdesivir group as compared to nonremdesivir group, though the difference was statistically insignificant ($p = 0.973$). This further suggests the protective effect of remdesivir against development of adverse cardiac event. It is believed that antiviral therapy is more efficacious if started earlier, and therefore, targeting moderate rather than severe disease would be a reasonable approach. In both the studies done by Spinner et al. and ACTT-1 trial, the benefit of remdesivir was more prominent in patients with less than 10 days of symptoms.^{19,22}

The length of ICU stay, hospital stay, and duration of invasive ventilation were significantly more in the remdesivir group (10.13 ± 7.48 , 14.13 ± 8.64 , 4.63 ± 6.00 , respectively), vs nonremdesivir group (6.58 ± 5.01 , 11.29 ± 8.64 , 1.80 ± 3.10 , respectively). Our results are in sync with the study done by Wang et al., in which they found that remdesivir administration was not associated with lesser time to clinical recovery, though it was numerically faster in patients who received remdesivir than patients who received placebo (21 vs 23 days).²³ Similarly, WHO Solidarity Trial Consortium have also failed to show benefit in mortality, initiation of ventilation, or hospitalization duration.²⁴ But in ACTT-1 trial, it was found that remdesivir administration has led to shorter recovery time and length of hospital stay (median, 12 vs 17 days) in comparison to placebo group.¹⁹ Most of these trials have recruited patients with mild, moderate, and severe disease, while in our study, we have recruited only critically ill patients requiring ICU admission; thus, more prolonged and complicated course is expected irrespective of remdesivir administration. These findings could be further interpreted as, though patients in remdesivir group have prolonged length of ICU and hospital stay, it has caused significant reduction in the incidence of MACE and MACE-related mortality, thus conferring overall protective effect.

The mechanism of action of remdesivir as an antiviral is to halt viral replication; thus, these trials support the use of remdesivir in the early active viral replication phase in COVID-19 patients.^{8,25-27} If patients progress from the viral replication phase to the inflammatory phase of infection, such as patients with ARDS requiring mechanical ventilation, remdesivir is not effective and anti-inflammatory drugs may be beneficial.

Incidence of acute kidney injury was significantly higher in patients who developed cardiac complications ($p < 0.0001$), but no difference was observed between remdesivir (39.6%) and nonremdesivir (60.4%) group ($p = 0.592$). A retrospective study of 3,993 patients hospitalized with COVID-19 infection, and acute kidney injury occurred in 46% patients with incidence (76%) in those patients who required ICU care (24%).^{28,29} The results of ACTT-1 trial showed the incidence of serious adverse effect in remdesivir group is 24.6% as compared to 31.6% in placebo group, with 16% incidence of acute kidney injury in remdesivir group and 20.3% in placebo group.¹⁹

However, efficacy of remdesivir has been studied in COVID-19 patients through worldwide trials, but its effect, particularly, on the incidence of major cardiovascular adverse effects and its correlation with mortality have not been studied yet, which is the main strength of our study. This point is more relevant due to the

fact that occurrence of MACE carries very high mortality risk in critically ill COVID-19 patients.

Our study has many limitations. First, due to the retrospective design, there is a possibility of missing some data. Further, due to the observational design, confounders like sepsis and acute kidney injury which has occurred after remdesivir administration during the course of illness could not be controlled and may have contributed to MACE. We did not administer remdesivir in any patient with chronic kidney disease due to its nephrotoxic potential. Third, we are unable to comment on the therapeutic efficacy of remdesivir in COVID-19. However, it is now recommended even in interventional studies to compare the effect of experimental drug with the standard treatment whenever possible, instead of placebo. Fourth, the modality of choice for diagnosis of myocarditis is cardiac MRI which usually suggests diffuse myocardial edema (in contrast to focal edema seen in non-COVID myocarditis), pericardial enhancement, and sometimes severe wall motion abnormalities. Since the facility was not available in our Institute, we were unable to determine the actual incidence of myocarditis. The actual incidence of myocarditis could not be determined due to nonfeasibility in availing cardiac MRI facilities in our Institute. Finally, the actual viral load in patients was not ascertained; thus, no comment can be made on antiviral activity of remdesivir.

In conclusion, this study of 437 critically ill COVID-19 patients admitted in ICU showed significant reduction in MACE and 28 day survival benefit in patients who received injection remdesivir in comparison to those who received standard treatment. However, several confounders like acute and chronic kidney disease, sepsis, severe ARDS, preexisting comorbid conditions like diabetes, and hypertension have to be taken into account before commenting upon the actual benefit of remdesivir on curbing the incidence of MACE in COVID-19 patients. Further prospective studies are warranted to affirm our findings and effect on other clinical outcomes.

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