ORIGINAL RESEARCH

Early use of remdesivir in patients hospitalized with COVID-19 and its effect on clinical outcome: An observational study from Rajasthan

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Abstract
Introduction: Remdesivir, a nucleotide analogue that competes ATP utilization with RNA dependent RNA Polymerase (RdRp) that interfere viral RNA polymerase that inhibit RNA synthesis and viral replication. It was widely used in patients of COVID-19 with different results in different stage of disease.
Methods: Present study is an observational cross sectional study to effect of remdesivir on patients of COVID-19 to compare early versus late use of remdesivir in hospitalized patients between 01/09/2020 to 10/09/2021.
Results: Total 99 cases of COVID-19 hospitalized at PMCH Udaipur during study period, the mean age of the patients was 58.26 years, majority were males (75%). Most Common presenting complaint was shortness of breath (67%). Hypertension (38%) was the most common morbidity. On clinical examination of patients 61% were febrile and 61% had tachypnoea. Overall, in hospital mortality observed was 22.22%. The lowest mortality (9.09%) was observed in group who received remdesivir in between 6-10 days of onset of illness while the group with initiation of remdesivir in between 1-5 days of illness had 26.67% mortality. The difference of mortality between of different group was found to be statistically significant(p=0.03). Whereas age, gender, underlying co morbidities, HRCT score before remdesivir administration did not show statistically significant association.
Conclusions: In our study, the use of remdesivir was found to be effective in early recovery and reducing mortality in patient of COVID-19 and best results were observed when remdesivir was initiated in early course of illness.
Key words: COVID-19; Remdesivir; HRCT chest; RT PCR; Pandemic

1. Introduction

The first unexplained pneumonia cases occurred in Wuhan, China, and quickly spread to other countries. It was later revealed that these unexplained pneumonia cases had been caused by a new coronavirus. It has been stated that the symptoms of this new coronavirus infection are very similar to those of SARS-CoV which spread in 2003[1]. Both act on the same receptor, namely the angiotensin-converting enzyme [2]. This virus is called SARS-CoV-2 and has been called by the WHO as the coronavirus disease 2019 (COVID-19) [2]. This virus cause acute respiratory distress syndrome(ARDS), acute lung injury, also pulmonary failure and death[3]. COVID-19, like SARS-CoV and MERS-CoV, also affects the nervous system. Remdesivir is a broad antiviral

nucleotide/nucleoside analogue, that inhibit viral replication which has activity against Ebola virus, Marburg, respiratory syncytial virus (RSV), Hepatitis C Virus (HCV), paramyxoviruses, MERS-CoV and SARS-CoV[4]. Remdesivir (GS-5734) prodrug nucleotide analogue which convert to nucleoside monophosphate, which is further phosphorylated to nucleoside triphosphate, its active form GS- 441524, that competes ATP utilization with RNA dependant RNA Polymerase (RdRp) that interfere viral RNA polymerase that inhibit RNA synthesis and viral replication[5].Remdesivir is administered as 200 mg loading on first day intravenous infusion over 30- 120 minutes, then maintenance 100 mg from next day to 10th day or till discharge or death. Indications of remdesivir are 1. Confirmed non severe COVID- 19, >40 kg and age> 12 year and highest risk of hospitalization, when alternative treatment not accessible or appropriate 2. Moderate to severe grade COVID-19, highest risk that lack COVID vaccination, older age and having co morbidity. It should be not recommended in children <12 year, weight <40 kg, renal impairment with eGFR < 30 ml/min, ALT ≥5x upper limit of normal and elevation in ALT/AST as accompanied by sign or symptoms of liver inflammation.

COVID-19 have three stages of clinical status, stage 1st (early infection), stage 2nd (Pulmonary phase 2nd A & 2nd B) and stage 3rd (hyper inflammation phase). Direct acting antiviral (DAA) drugs acts in stage 1st and stage 2nd (early phase)[6]. Viral response phase is up to 2nd stage. Stage 1st is up to 5 days from onset of symptoms, 2nd stage 6 to 10 days and third stage 3rd more than 10 days[7].

2. Objectives

1. To determine the comparative efficacy of remdesivir in hospitalized adult patients of COVID-19 in Pacific Medical College and Hospital, Udaipur in between 1st September 2020 and 10th September 2021 in different groups based upon day of initiation of remdesivir.
2. The efficacy was compared in terms of time taken for conversion RT PCR report, need of additional treatments, and mortality pattern in various groupsof patients.

3. Methods

The current study is an observational cross sectional study based on data collected to compare the effect of early versus late use of remdesivir on prognosis of COVID-19 in tertiary care center at PMCH Udaipur Rajasthan.

Study Design

In the present study, COVID- 19 patients who admitted from 1st September 2020 to 10th September 2021 were included. Patients were divided into two groups depending upon the time of initiation of remdesivir treatment early (1 to 15 days) and late

group (after 15 days). Early group is subdivided into three groups 1st (1 to 5 days), 2nd (6 to 10 days), 3rd (11 to 15 days). The study population was divided in to three groups depending upon chest CT finding. HRCT chest has been performed using 5 mm slice thickness cuts in axial plane use scoring system range from 0 to 25. There are 5 lung lobes (right upper, right middle, right lower, left upper and left lower lobe). Each lobe having score 0 to 5. As 0 = no; 1 = < 5%; 2 = 5-25%; 3 = 26 – 49%; 4 = 50 – 75%; and 5 = > 75% involvement[8]. Classification of COVID HRCT severity score as mild grade if ≤ 8 score, moderate grade = 9-15 score and severe grade if > 15 score.

Inclusion criteria

1. COVID-19 RT PCR positive.
2. Radiological (HRCT chest) finding suggestive of COVID-19.
3. Patients who received remdesivir

Exclusion criteria

1. Asymptomatic patients <18 years age.
2. Pregnant and nursing mothers.
3. OPD patients.
4. Home isolation

Late use of remdesivir was considered after 15 days of onset of symptoms. Patients who have moderate to severe disease were administered remdesivir as 200 mg loading dose on first day, followed by a 100 mg as maintenance dose next four days intravenously with other standard care like steroids (methylprednisolone/dexamethasone), enoxaparin, IV antibiotic as per hospital protocol according to PMCH in accordance with the ICMR guidelines.

Use of other drugs like Ivermectin, hydroxychloroquine, vitamin C, zinc, doxycycline, azithromycin, oseltamivir, tocilizumab/ itolizumab, N-acetyl cysteine, pirfenidine, plasma therapy were administered as per the clinical judgment of the treating physician in concurrence with the recommendations of PMCH and ICMR guidelines.

Outcome measures

The outcomes were measured by analysis of 1. Time taken for conversion from positive to negative RT PCR report, 2. Need of additional treatments like tocilizumab & plasma therapy required, 3. Mortality pattern in various groups of patients. Data on laboratory and clinical findings like CBC, LFT, RFT, RBS, chest CT severity scores, chest X-ray, inflammatory markers were recorded and analyzed. Demographic data like age, sex and comorbities like diabetes, hypertension, IHD, CKD, CVA, hypothyroidism, asthma were also assessed.

Statistical Analysis

The data of COVID-19 patients was collected in Microsoft office excel 2007 sheet. Table, charts were made with help of Microsoft word and excel. Statics

like mean, standard deviation were calculated using excel sheet. Chi square and P-value were calculated online by socscistatistics.com and mathsisfun.com site. P value < 0.05 was considered significant.

4. Results
Total 99 COVID-19 patients were hospitalized during study period, the mean age was 58.26 years and majority of patients (75%) were male.

Table 1:Distribution of demographics and clinical characteristics of different groups of remdesivir therapy

Groups		1st (1 to 5 days)	2nd (6 to 10 days)	3rd (11 to 15 days).	P Value
No of patients (99)		60	33	5	
Age (Mean)		59.21	57.21	51.8	
Sex ratio		3.62	3.13	0.67	
No. of Comorbidities*		58	42	3	
Clinical Severity					
1.Spo2	<90%	35(58.3%)	19(57.6%)	2(40%)	
2.CT severity	Mild ≤ 8/25	9(15%)	4(12.1%)	1(20%)	0.95
	Moderate 9/25-15/25	21(35%)	12(36.4%)	2(40%)	
	Severe >15/25	24(40%)	16(48.5%)	2(40%)	
3.Need of mechanical ventilation		8(13.3%)	1(3%)	0	

*More than one comorbidity in single patient

In present study, mean age in three different groups were 59.21, 57.21, and 51.8 respectively while sex ratio in different groups were 3.62, 3.13 and 0.67 respectively. Clinical severity by Spo2 at admission were almost similar in group 1st (58.3%) an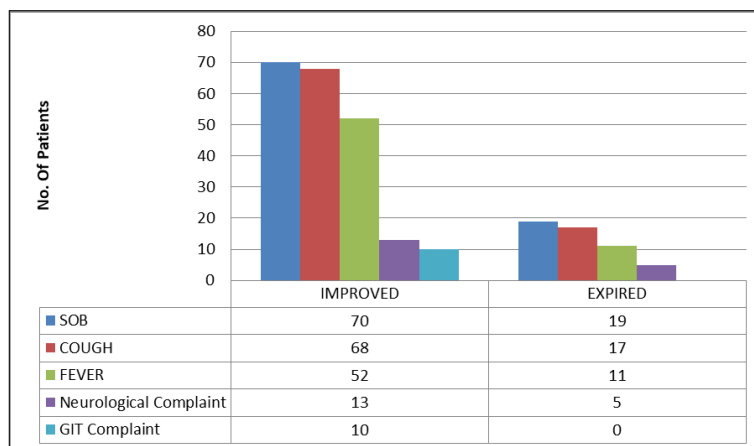d 2nd (57.6%). There was no statically significant difference in chest CT severity score of different groups (P=0.95). The case severity as per need of mechanical ventilation the group 1st had more number of serious patients (Table 1).

Table 2: Clinical profile at admission

Vital parameters	
Febrile	61
Afebrile	38
Respiratory Rate	
Normal	38
Tachypnoea	61
*Blood Pressure (mmHg)	
Systolic blood pressure	130.68±21.32
Diastolic blood pressure	78.67±11.21
Pulse Rate (bpm)	
>100	43
60-100	52
SPO2 %	
> 94%	22
≤ 94%	77
Chief Complaint	
SOB	67
Cough	64
Fever	62
Neurological	18
Gastrointestinal	10

The most common symptoms being shortness of breath (67%), followed by cough (64%), fever (62%) and neurological presentation (18%) while 10% of the patients having gastrointestinal symptoms and oral ulcer (Table 2).
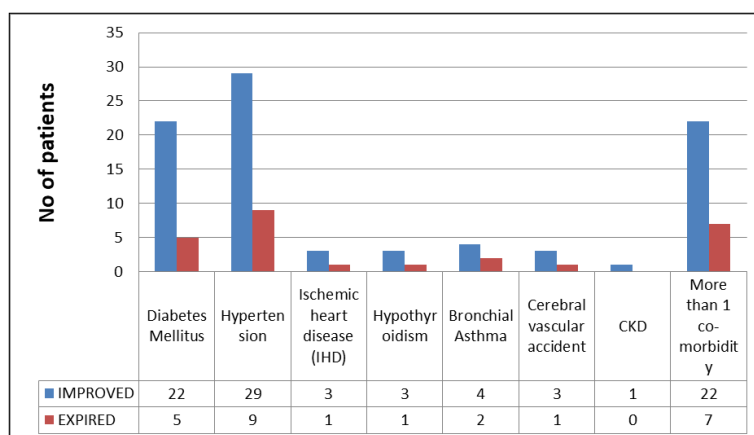
Maximum mortality was seen in patients having symptoms shortness of breath (86.36%), followed by fever (50%), and then neurological manifestations (22.27%) (Fig.1).

	IMPROVED	EXPIRED
■ SOB	70	19
■ COUGH	68	17
■ FEVER	52	11
■ Neurological Complaint	13	5
■ GIT Complaint	10	0

Fig.1 Frequency of COVID-19 patients improved/cured and expiredaccording to different sympotoms

Most common comorbidity was hypertension (38%), followed by diabetes mellitus (27%), bronchial asthma (6%), IHD (4%), cerebral vascular accident (4%), hypothyroidism (4%), CKD (1%), and sleep apnea (1%), while 29% patients having more than one comorbidity. The highest mortality was observed in patients with multiple comorbidity (24.13%), followed

by hypertension (23.68%) and diabetes mellitus (18.5%) (fig. 2). Out of 99 patients, 22 patients did not require supplementary oxygen but 77 patients required supplementary oxygen. Oxygen was delivered through nasal prong, face mask, non re-breathable face mask, NIV and invasive mechanical ventilation. 10 patients required oxygen by ventilator.

	Diabetes Mellitus	Hypertension	Ischemic heart disease (IHD)	Hypothyroidism	Bronchial Asthma	Cerebral vascular accident	CKD	More than 1 co-morbidity
■ IMPROVED	22	29	3	3	4	3	1	22
■ EXPIRED	5	9	1	1	2	1	0	7

**Fig2: Comorbidities in relation to survival and mortality of COVID-19 patients**

As per the chest CT severity score, out of 99 patients, 91 patients were satisfied radiological criteria required for severity scoring, These were classified as mild

grade 14 patients, moderate grade 35 patients and severe grade having 42 patients (fig. 3).
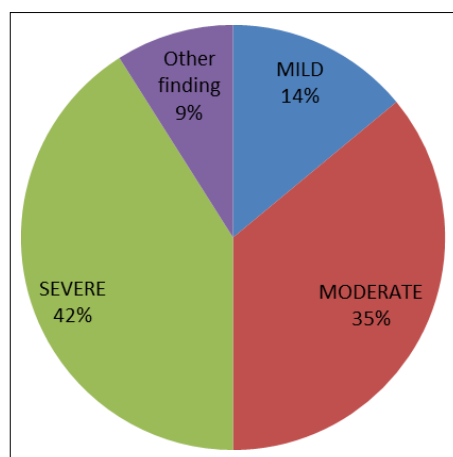
Fig. 3 Showing CT chest severity grading of COVID 19 patients

Mean CT severity score was 13.97±5.22. Most common CT finding was ground glass opacity (fig. 4) and other finding like crazy paving, subpleural band, consolidation, interseptal thickening, enlarge lymph node.
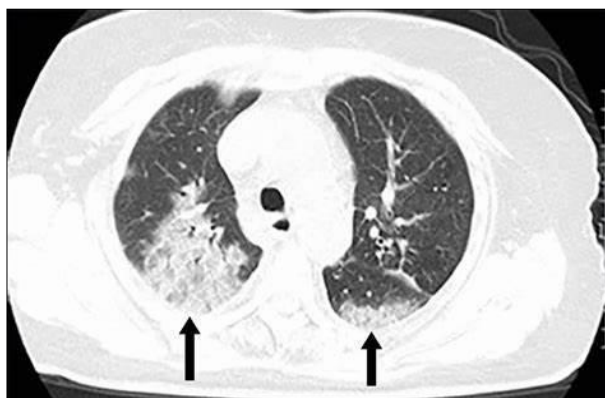
Fig. 4 CT Chest showing ground glass opacity

Table 3: Inflammatory markers

	Min.	Max.	Mean ± SD
CRP (mg/L)	1.1	367	93.14 ± 86.38
ESR (mm/hr)	10	280	41.84 ± 33.68
IL-6 (pg/mL)	1.2	792	118.13 ± 150.36
FERRITIN (ng/mL)	67	>2000	515.15 ± 365.51
D-DIMER (ng/mL)	115	>4000	1347.20 ± 1040.05
LDH (U/L)	5	1910	427.67 ± 252.77

Inflammatory markers like CRP, ESR, IL-6, ferritin, D- dimer, and LDH were highly raised in COVID-19 patients. Mean value of CRP= 93.14 mg/l, ESR = 41.84 mm/hr, IL-6=118.13 pg/ml, ferritin = 515.15 ng/ml, D dimer = 1347.20 ng/ml, and LDH = 427.67 U/L were found in COVID-19 patients (Table 3).

Table 4: Response of remdesivir on survival and mortality in relation to period of administration

On which day of onset symptoms remdesivir administered	Total patients	Death		Survive		Chi-square	P Value
		No	%	No	%		
≤ 5	60	16	26.67	44	73.33	8.392	0.039
6-10	33	3	9.09	30	90.91		
11-15	5	2	40	3	60		
≥16	1	1	100	0	0		

Out of 99 remdesivir received only 22 patients expired that is mortality was noted in 22.22% cases out of which maximum 100% patients expired who got remdesivir after 15 days onset of symptoms, followed by 40% expired who got remdesivir in between 11-15 days of onset of symptoms, then 26.67% expired who got remdesivir within 5 days and 9.09% expired who got remdesivir in between 6-10 days of onset of symptoms (table 4). In table 4, result of the duration and survival versus non-survival is significant, but small issue is that some of the cell frequencies are very low (< 5).

Table 5: Response of remdesivir on survival and death in relation of different chest CT severity groups of patients and period of administration

	Mild(14)		Moderate(35)		Severe(42)		P Value
Group	Death	Survive	Death	Survive	Death	Survive	
1st	2	7	2	19	10	14	0.85
2nd	0	4	0	12	3	13	
3rd	0	1	1	1	1	1	

The mortality pattern in different group of remdesivir treatment (day of initiation) had shown lowest mortality in group 2nd irrespective of CT severity (Table 5)

Early conversion of COVID-19 RT PCR from positive to negative being maximum (66%) within one week,

followed by 28% in two weeks and 6% in three weeks (Fig. 5). Tocilizumab was given in four patients out of which three expired. Bevacizumab given to one patient, that also expired.
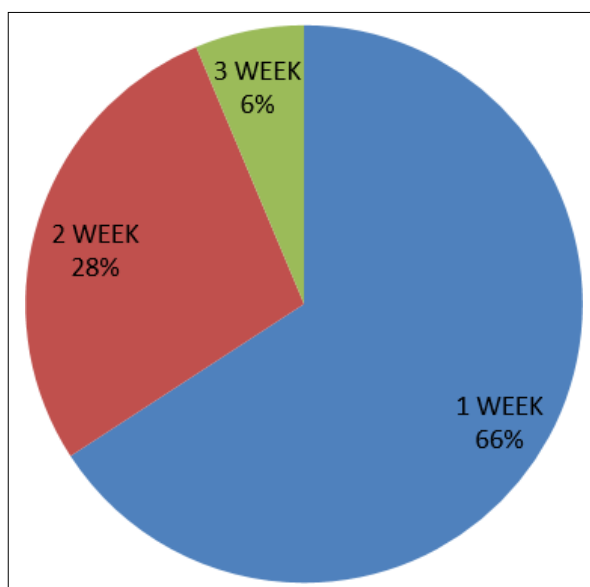

Fig 5 Relative share of COVID-19 positive patients becoming negative according to time

Table 6: Outcome in different subgroups of patients received remdesivir

		N	Death No.	Death %	Survive No.	Survive %	C2	P
All patients		99	22	22.22	77	77.77		
Sex	Male	75	17	22.67	58	77.33	0.035	0.85
	Female	24	5	20.83	19	79.17		
Age group	≤30 yrs	3	1	33.33	2	66.67	5.21	0.74
	31-60 yrs	57	8	14.03	49	85.97		
	≥61 yrs	39	13	33.33	26	66.67		
No of comorbidity	0	41	9	21.95	32	78.05	4.038	0.5438
	1	26	5	19.23	21	80.77		
	2	20	4	20	16	80		
	3	7	2	28.57	5	71.43		
	4	3	2	66.67	1	33.33		
	5	1	0	0	1	100		
HRCT before remdesivir	Mild	14	2	14.29	12	85.71	8.39	0.015
	Moderate	35	3	8.57	32	91.43		
	Severe	43	15	34.88	28	65.12		

The patients who received remdesivir among them mortality was 22.22%, slightly higher in males 22.67% and moderately high in elder 33.33% and ≤ 30 year age 33.33% (Table 6).

4. Discussion

The first unexplained pneumonia case occurred in Wuhan city of China in 2019, later on known that was caused by Corona virus[9]. This COVID-19 spread in many countries and became pandemic. Many deaths were occurring in china and other countries that were not under control, so all were afraid because of this

infection. In India a first COVID-19 case 20 year female presented with dry cough and sore throat in emergency department of general hospital, Thrissur, Kerala on January 27, 2020. This infection spread in India in just few months. There were no specific treatment available, and no vaccine available for prevention. Many studies were conducted to control COVI-19 during pandemic to find out specific treatment and vaccine so that pandemic can be controlled. 99 COVID- 19 patients admitted to PMCH Udaipur from 1st September 2020 to 10th September 2021 were evaluated to find out impact of early versus

late use of remdesivir on survival and mortality. Out of 99 cases of COVID-19 in present study at PMCH Udaipur, 81 cases were RT PCR positive and remaining 18 patients were included in study on the basis of chest CT suggestive of COVID-19. 68 COVID-19 RT PCR positive admitted in ICU and 13 were COVID-19 RT PCR positive admitted in ward. While 18 patients with RT PCR negative having chest CT suggestive of COVID admitted ICU. The mean age of study population was 58.26 years, majority (75%) were males. In our study shortness of breath (67%) was found to be most common presentation, followed by cough (64%), and fever (62%) while 8% patients having neurological presentation like headache (6%), loss of consciousness (6%), hemi paresis (3%), slurring speech (3%) , ascending paralysis (GBS) 1%, irrelevant talk (1%), and convulsion (1%). 10% patients having GIT complaint like nausea, vomiting, diarrhea, loss of appetite, constipation, and oral ulcer. In a study by Esakandari H *et al* in 2020[10]. that admitted patients with complain of difficulty in breathing, chest pain, and loss of speech or movement that required urgent management. These shows that mainly affected system are respiratory followed by nervous system. Most of Chest x- ray of COVID-19 patients shows opacity in lower zone outer side (Fig. 6). In study of (Tian S, 2020)[11]. Chest X-rays show pneumonia having bilateral ground glass opacity seen in outer and peripheral lung field. So on the basis of chest X ray finding, we can suspect COVID-19 infection.

Fig. 6 Chest x ray of COVID-19

In our study population the mortality was 22.22%, which is slightly higher in males (22.67%). and the mortality was high in elderly (>60 years) and younger patients (< 30 year). In a similar study by Ganesh Manudhane *et al* in 2021[12] reportedtotal mortality was 18.5%, significant higher in elder and slight higher in males. Most common comrbidity was hypertension, followed by diabetes and ischemic heart disease. Mortality was slightly higher in our study because it include higher number of patients who need ICU care (Table 5). In our study most commonly morbidities were hypertension, diabetes and bronchial asthma and then ischemic heart disease.

In our study maximum mortality (100%) was in late use mean administration of remdesivir after 15 days of onset of symptoms and minimum mortality was in group of patients remdesivir administered between 6- 11 days and P value is 0.0385 (<0.05) means results are significant. So it shows that early use of remdesivir is helpful in saving life of COVID -19 patients.

In study of (Vishal Gupta1, 2021)[13] mortality was significantly low when remdesivir and tocilizumab both administered. But in our study mortality did not

Decrease because tocilizumab given only to four very critical ill patients out of which three expired. This study has limitations like that there was no control group because it was not ethically possible because during study period, there were guideline to give remdesivir. We could not correlate response of remdesivir and inflammatory markers because inflammatory markers done once only as per requirement due to financial reason. Hence further study would be required.

5. Conclusions

In our study it was observed that use of remdesivir was found to be effective in early recovery and reduction in mortality irrespective of age, gender and comorbidity in patient of COVID-19 and best results were observed when remdesivir in early course of illness. So remdesivir should be administered in COVID-19 patients early as possible for better outcome.

6. Declarations
   Ethics approval and Consent to participate:
There are no sensitive data, and no patients were

recruited for this study. The authors accept the full transfer of copyright to the journal.

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