Journal of Advanced Research in Medicine
Volume 9, Issue 4 - 2022, Pg. No. 11-18
Peer Reviewed & Open Access Journal

Research Article

A Study to Analyse the Effect of Remdesivir on Clinical and Immunological Profiles in Moderate COVID-19 Patients

Rajesh Jakhar[1], Sandeep Garg[2], B. C. Koner[3], Sunita Aggarwal[4], Praveen Bharti[5], Namita George[6], Deepak Ranjan Malla[7]

[1,6,7]Post Graduate student, Department of General medicine, MAMC & Lok nayak hospital delhi,India.
[2,4]Director & Professor, Department of general medicine, MAMC & Lok nayak hospital delhi,India.
[3]Head of Department, Department of Biochemistry, MAMC Delhi,India.
[5]Associate professor, Department of General Medicine, MAMC & Lok nayak hospital delhi,India.
DOI: https://doi.org/10.24321/2349.7181.202216

I N F O

Corresponding Author:
Rajesh Jakhar, Post Graduate student, Department of General medicine, MAMC & Lok nayak hospital delhi,India.
E-mail Id:
rajeshjakhar37@gmail.com
Orcid Id:
https://orcid.org/0000-0001-6298-9086
How to cite this article:
Jakhar R, Garg S, B C Koner, Aggarwal S, Bharti P, George N, Malla R D .J Adv Res Med 2022; 9(4): 11-18.
Date of Submission: 2022-10-13
Date of Acceptance: 2022-11-30

A B S T R A C T

Introduction: COVID-19, caused by SARS-CoV-2, has become a global pandemic. Various drugs have been used to manage this disease.

Aim: This study examines the effect of remdesivir on clinical and immunological profiles in moderate COVID-19 patients.

Methods and Material: This prospective cross-sectional study was conducted at Maulana Azad Medical College. We enrolled 50 moderate COVID-19 patients without renal or hepatic disease. Patients received daily remdesivir for 5 days and were monitored for 7 days. Clinical assessment used NEWS 2 scoring, and immunological profiles were measured by IL-6, CRP, D-dimer, PCT, and serum ferritin tests. Data were analyzed with SPSS version 25 and Pearson correlation.

Results: Remdesivir improved clinical and immunological profiles. NEWS 2 scores improved over 7 days. CRP and IL-6 levels decreased, while D-dimer, procalcitonin, and ferritin trends varied between recovered and worsening patients. D-dimer, serum ferritin, and procalcitonin levels improved in moderate cases but worsened in severe cases.

Conclusion: NEWS 2 score was an effective clinical status marker. CRP, IL-6, D-dimer, and serum ferritin were reliable disease severity markers, higher in severe and deteriorating patients. PCT was useful for early bacterial infection detection. The relevance of remdesivir in COVID-19 outcomes remains debated, with mixed study results.

Keywords: COVID-19, SARS-CoV-2, NEWS-2, IL-6, CRP, D-dimer, PCT

Introduction

Coronaviruses (CoV) are enveloped viruses that cause respiratory infections in human beings.[1] A novel coronavirus called SARS-CoV-2 was identified in Wuhan, China in December 2019 as the pathogen responsible for coronavirus disease (COVID-19).[2] The World Health Organization declared COVID-19 a pandemic on March 11, 2020.

SARS-CoV-2 negatively impacts the respiratory tract and lungs.[3] Septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS) can be seen in severe cases of COVID-19.[4] Age, as well as pre-existing conditions like cancer, hypertension, diabetes mellitus, and cardiovascular diseases cause a person to be at a higher risk for developing a severe case of COVID-19, and a higher risk of mortality.[5,6]

The mortality rates seen in COVID-19 patients are considerable and wide-ranging (1.4%–15%).[4–8] Several candidate drugs like chloroquine, hydroxychloroquine, remdesivir and favipiravir were considered and evaluated for treatment in COVID-19 patients.[9] In this study, we aimed to find the effect of remdesivir on clinical and immunological profiles in moderate COVID-19 patients.

Methodology

Subjects and Methods

It was a prospective cross-sectional study which was conducted by recruiting newly diagnosed COVID-19 patients admitted to the medicine wards of Lok Nayak Hospital, New Delhi from January 2021 to December 2021. A total of 50 patients who fulfilled the inclusion as well as exclusion criteria were included in the study. A detailed history of the participants was taken. Clinical examination was done on these patients regarding the severity of COVID-19 and renal and hepatic diseases. These patients were subjected to NEWS 2 scoring and routine investigations like haemogram, KFT, LFT, serum electrolytes, CXR, CRP, serum ferritin, IL-6, PT-INR, APTT and D-dimer were done. These patients were continued on the standard of care treatment and a 5-day course of remdesivir and were followed up for clinical and immunological outcomes.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) version 25 was used for the processing of data. Continuous variables were shown in the form of mean and standard deviation. Student t test was used to compare them. Categorical variables were shown in the form of frequencies and percentages. The chi-square test was used to compare them. A p value of less than 0.05 was considered to be significant for all statistical tests. The correlation between the immunological and clinical parameters of COVID-19 was analysed by the Pearson correlation coefficient.

Results

The patients recruited in the study were between the ages of 18 and 65 years and of either gender. The mean age of our study population was 50.92 ± 12.03 years. Most of the patients were in the age group of 51–60 years, of which 66% (33) were male and 34% (17) were female. The most common presenting complaint was shortness of breath which was present in all except one patient. Fever was present in 82% of the patients. The common respiratory complaints after shortness of breath were cough and chest pain. Upper respiratory involvement included anosmia (16%) and sore throat (4%). Abdominal and neurological symptoms were limited. Out of 50 patients, 5 patients had no comorbidities on presentation. Thirteen patients had one comorbidity, while 21 and 2 patients had two and more than two comorbidities, respectively. Hypertension was the most common, followed by diabetes mellitus (Table 1). The patients were followed up till day 7 of admission. The complications were observed in 17 patients, with at least one complication present in 10 patients. Three patients had more than two complications. Sepsis developed in 13 of the 17 patients with complications (Table 2).

Table 1.Frequency of Comorbidities

Comorbid Conditions	Frequency	Percentage
Hypertension	22	44.0
Diabetes mellitus	17	34.0
Hypothyroid	5	10.0
Coronary artery disease and ischaemic cardiomyopathy	13	26.0
Alcohol	4	8.0
Smoker	9	18.0
Old treated pulmonary Koch's	5	10.0
Anaemia	3	6.0
Morbidly obese	3	6.0
Cerebrovascular accident	2	4.0
Other	10	20.0

ISSN: 2349-7181
DOI: https://doi.org/2010.24321/2349.7181.202216

Table 2.Frequency of Complications During Treatment

Complications	Frequency	Percentage
Sepsis	13	26.0
Myocardial infarction	4	8.0
Acute kidney injury	3	6.0
Respiratory failure	3	6.0
Acute liver failure	1	2.0
Coagulopathy	1	2.0
No	33	66.0

Regarding the outcome of these patients, three patients could not survive the illness but completed the study duration of 7 days. Thirty-three patients were discharged from the ward itself, while 14 patients who were transferred to the ICU in view of deterioration were also discharged upon recovery. This is shown in Figure 1.

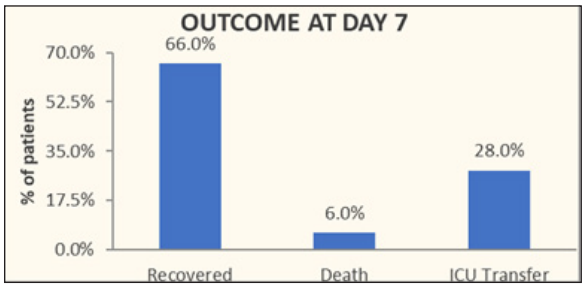

Figure 1.Final Outcome at Day 7

To assess the clinical state of the patients, we employed the NEWS 2 score. It was calculated every day for all seven days. On the day of admission, according to the NEWS 2 scoring, 19 patients were categorised in the moderate group (ranging from 5 to 7) and 31 patients in the severe group (more than 7). All these patients were continued on the standard of care treatment and a 5-day course of remdesivir and were followed up for NEWS 2 scoring on a daily basis. From day three onwards, patients' clinical states began to improve. Ten patients improved to the mild group in total, whereas 11 patients from the severe category improved to the moderate or mild categories. Six more patients improved from moderate to mild on day 4. Day 5 was the day of the last remdesivir dose, and our study showed 33 individuals on the path of recovery; all of them were in the mild group, which continued on day 7.

The 17 patients who did not improve in their NEWS 2 score by day 3 of therapy were transferred to critical care as their oxygen requirement was increasing. On day 3, there were still two patients in the severe group who were being monitored in the ward as their scores were improving, and these patients improved to the mild category by day 5. Out of the 17 patients who were transferred to the ICU, 14 improved following their stay, however, three passed away as a consequence of the disease (Table 3).

Table 3.Progression of NEWS 2 Score During Hospital Stay

Days	Clinical Condition (NEWS 2)							
	Mild		Moderate		Severe		Total	
	n	%	n	%	n	%	n	%
Day 1	0	0.0	19	38.0	31	62.0	50	100.0
Day 2	0	0.0	20	40.0	30	60.0	50	100.0
Day 3	10	20.0	21	42.0	19	38.0	50	100.0
Day 4	16	32.0	15	30.0	19	38.0	50	100.0
Day 5	33	66.0	0	0.0	17	34.0	50	100.0
Day 6	32	64.0	1	2.0	17	34.0	50	100.0
Day 7	33	66.0	0	0.0	17	34.0	50	100.0

Regarding the immunological profile of patients, on day 1, the mean CRP was 23.85 ± 14.32, which improved to 17.33 ± 13.99 and 15.52 ± 16.52 on days 5 and 7, respectively, all of which were statistically significant. The mean IL-6 on day 1 was 21.03 ± 13.11, and it gradually declined during the hospital stay. However, the decreases in mean IL-6 on days 3 and 5 were not statistically significant. On day 1, the mean D-dimer concentration was 1565.36 ± 1608.88 ng/mL. It increased with each successive day, finally reaching 3369.85 ± 6168.15 ng/mL on day 7. The mean procalcitonin level on day one was 1.40 ± 1.41 ng/mL. It increased with each passing day, finally peaking at 10.82 ± 25.17 ng/mL on day 7. On the day of admission, the mean serum ferritin level was 630.10 ± 349.44 ng/mL, and it gradually climbed to 751.00 ± 721.52 ng/mL on day 7 (Table 4).

Table 4.Changes in Immunological Markers During Hospital Stay

Immunological Marker	Mean on Day 1	Mean on Day 7
CRP (ng/mL)	23.85 ± 14.32	15.52 ± 16.52
IL-6 (pg/mL)	21.03 ± 13.11	16.31 ± 17.97
D-dimer (ng/mL)	1565.36 ± 1608.88	3369.85 ± 6168.15
Serum ferritin (ng/mL)	630.10 ± 349.44	751.00 ± 721.52
PCT (ng/mL)	1.40 ± 1.41	10.82 ± 25.17

ISSN: 2349-7181
DOI: https://doi.org/2010.24321/2349.7181.202216

In our study, a larger percentage of patients recovered as a result of the therapy. Concurrently, the mean CRP and IL-6 levels decreased with medication, while the mean D-dimer, procalcitonin, and ferritin levels continued to rise on each subsequent day. We attempted to investigate this confounding effect by computing the mean values of the markers of patients in the moderate and severe categories individually. As shown in Table 5, the mean D-dimer, procalcitonin, and ferritin levels in the moderate category patients declined by day 7, however, they increased in the severe category patients.

When the mean D-dimer of the moderate category patients according to NEWS 2 scoring was measured, it decreased from 1517.89 ng/mL on admission to 1136.38 ng/mL on day 7. In the same time period, the mean D-dimer of patients in the severe category increased from 1582.19 ng/mL to 3688.58 ng/mL. When the mean procalcitonin of the moderate patients was measured, it decreased from 1.31 ng/mL on admission to 0.92 ng/mL on day 7. For patients in the severe group, the mean procalcitonin increased from 1.46 ng/mL to 8.85 ng/mL over the same time period. The mean serum ferritin levels decreased in patients in the moderate category according to NEWS 2 scoring from 654 ng/mL on day 1 to 565 ng/mL on day 7 and increased in patients in the severe category from 611.58 ng/mL on day 1 to 818.96 ng/mL on day 7, following a similar linear trend as shown by D-dimer and procalcitonin levels.

Table 5.Mean of Inflammatory Markers in Moderate and Severe Category Patients on Day 1 and Day 7

Immunological Marker	Moderate Patients		Severe Patients	
	Day 1 mean	Day 7 mean	Day 1 mean	Day 7 mean
CRP (ng/mL)	24.47	10.04	23.29	18.71
IL-6 (pg/mL)	20.78	13.73	22.04	16.92
D-dimer (ng/mL)	1517.89	1136.38	1582.19	3688.58
Serum ferritin (ng/mL)	654.00	565.00	611.58	818.96
Procalcitonin (ng/mL)	1.31	0.92	1.46	8.85
Prothrombin time (sec)	18.10	17.58	22.10	23.70
INR	1.12	1.10	1.13	1.20
aPTT (sec)	27.94	26.20	28.12	29.10

Discussion

The NEWS 2 score was used to assess the clinical status of the patients. NEWS 2 score is the latest version of the NEWS score, which advocates a system to standardise the assessment and response to acute illness. It consists of systolic blood pressure, heart rate, temperature, respiratory rate, oxygen saturation, use of supplemental oxygen, and level of consciousness. It was computed every day for seven days. We had 19 patients in the moderate category (5–7) and 31 in the severe category (> 7) on the first day according to NEWS 2 scoring. In a comparable study (sample size = 35) by Antinori et al., 17 patients were classified as moderate (mean NEWS 2 score was 5) and 18 patients as severe (mean NEWS 2 score was > 7).[10] In a phase 3, open-label, multicenter, randomised controlled study with a sample size of 857 patients, 61% were in the moderate group on presentation, while 39% were in the severe category.[11]

By day 7, 33 patients (66%) improved to the mild category (all 19 moderate group patients and 14 severe group patients) and were discharged. 17 patients remained in the severe group, and 14 of them were discharged from the ICU. Sixt et al. investigated the utility of NEWS 2 at day 7 of hospitalisation in predicting COVID-19 outcomes in 222 patients. They computed NEWS 2 at admission and on day 7 (excluding the patients who died within the first seven days of hospitalisation). There were 134 mild, 18 moderate, and 11 severe patients among the 170 patients that survived on day 7. From day one, there was an improvement in 79% of the patients.[12] The disparity in the improvement percentage is explained by the higher number of patients in the mild category at the start of the study.

Our study had a mean CRP of 23.85 ± 14.32 on day 1, which improved to 15.52 ± 16.52 on day 7, all of which were statistically significant. Stoeckle et al. studied 55 patients

ISSN: 2349-7181
DOI: https://doi.org/2010.24321/2349.7181.202216

who had been treated with remdesivir for COVID-19 and then analysed their inflammatory markers as well as clinical outcomes. Their main outcome was whether the patients were alive and non-intubated (non-progressors) or dead by day 14 (progressors) or on mechanical ventilation. C-reactive protein (CRP) was found to be higher in patients who were intubated or dead by day 14 as compared to those who improved. Among the patients who were non-intubated over the study period, the administration of remdesivir significantly lowered the CRP levels.[13]

On day one, the mean IL-6 level was 21.03 ± 13.11, and it significantly decreased during the hospital stay. Our study showed a statistically significant reduction in IL-6 by day 7. Our findings are in concurrence with the findings of Stoecke et al. They also observed a drop in IL-6 in patients on remdesivir who were recovering, but it increased in patients who were transferred to the intensive care unit or died. Higher IL-6 levels in severe patients support the notion that COVID-19 is a hyperinflammatory condition linked with a rise in pro-inflammatory cytokines and that elevated inflammatory markers are related to a severe course of disease and a poor eventual outcome.[13]

On day 1, the mean D-dimer concentration was 1565.36 ± 1608.88 ng/mL. It increased with each successive day, finally reaching 3369.85 ± 6168.15 ng/mL on the last day. When the mean D-dimer of the moderate category patients according to NEWS 2 scoring was measured, it decreased from 1517.89 ng/mL on admission to 1136.38 ng/mL on day 7. In the same time period, the mean D-dimer of patients in the severe category increased from 1582.19 ng/mL to 3688.58 ng/mL. Stoeckle et al. investigated inflammatory markers and clinical outcomes in 55 patients. Their key outcome was whether patients were on mechanical ventilation, or died by day 14 (progressors), or remained alive, or did not need intubation (non-progressors). According to their findings, the median D-dimer was substantially greater in progressors than in non-progressors (871 vs 576). The patients who were improving showed a decreasing tendency in their D-dimer readings, whereas severe patients had the opposite trend.[13] Therefore, D-dimer levels can indicate severe and catastrophic outcomes in COVID-19 patients.

The mean procalcitonin level on day one was 1.40 ± 1.41 ng/mL. It increased with each passing day, finally peaking at 10.82 ± 25.17 ng/mL on day 7. When the mean procalcitonin of the moderate patients was measured, it decreased from 1.31 ng/mL on admission to 0.92 ng/mL on day 7. For patients in the severe group, the mean procalcitonin increased from 1.46 ng/mL to 8.85 ng/mL over the same time period. Richardson et al. performed a case series across 12 hospitals in New York that comprised 5,700 COVID-19 patients. At the time of admission, the average procalcitonin level was 0.2 ng/mL.[14] Mazaheri et al. examined inflammatory markers using procalcitonin in 76 COVID patients (46 ICU patients and 30 non-ICU patients) and discovered that PCT was considerably greater in ICU patients (0.65 vs 0.18, p = 0.001). The higher PCT group showed higher values of TNF (p = 0.01) and a longer ICU stay among 46 ICU patients.[15] A meta-analysis of four studies found that higher PCT concentrations were linked to more severe COVID-19 infection. PCT may stay within normal reference ranges in persons with uncomplicated COVID-19. The authors hypothesised that high PCT in individuals with severe COVID-19 may be due to bacterial superinfection.[16] In the Indian research done by Parimoo et al., the median procalcitonin level was 0.73 ng/mL among non-survivors and 0.15 ng/mL among survivors, indicating that increased procalcitonin levels were related to a worse outcome (p = 0.005).[17]

On the day of admission, the mean serum ferritin level was 630.10 ± 349.44 ng/mL, and it gradually climbed to 751.00 ± 721.52 ng/mL on day 7. The mean serum ferritin levels decreased in patients in the moderate category according to NEWS 2 scoring (from 654.00 on day 1 to 565.00 on day 7) and increased in patients in the severe category (from 611.58 on day 1 to 818.96 on day 7). The AIIMS study discovered that the median ferritin level was 1009 ng/mL at baseline in non-survivors compared to 659 ng/mL in survivors. This difference was found to be statistically significant. The median ferritin level before the terminal event (survival or death) was 1395 ng/mL in non-survivors and 600.5 ng/mL in survivors, which showed a statistically significant difference (p = 0.001).

Inflammatory markers like CRP, IL-6, D-dimer, procalcitonin, and ferritin have predictive relevance in COVID-19 patients. A rise in these markers of inflammation is an early sign of a cytokine storm. This has been found to be associated with a poor prognosis and high mortality in COVID-19.

Thirty-three patients were discharged from the ward, while 14 patients who were moved to ICU due to deterioration were also discharged on recovery. Three people died (6%) as a result of the disease. Beigel et al. reported a little higher death rate of 11% (59 out of 541) than we did (6%).[18] Suresh et al. recruited 116 participants in their study and found a considerably increased death rate. In their study, 50 individuals did not survive the sickness.[19] The difference might be explained by a greater number of individuals with severe illness on presentation (72% in their study versus 62% in our study).[14] In our study, 28% of patients required ICU care, compared to 14% of patients in a case series from 12 New York hospitals.[14]

Remdesivir's effect on COVID-19 patients remains a mystery to this day, since no study or meta-analysis has clearly demonstrated a substantial improvement in outcomes, nor

ISSN: 2349-7181
DOI: https://doi.org/2010.24321/2349.7181.202216

has any study clearly stated that it is of no help. Studies done by Spinner et al. and Beigel et al. previously triggered the FDA's emergency approval of this medicine.[20] They came to the conclusion that using remdesivir improves clinical outcomes, minimises complications, dampens abnormal immune responses, and lowers mortality. Remdesivir had an acceptable safety profile, according to research done in Indian settings by Gupte et al. The clinical improvement rate was 84%, with patients over the age of 60 years getting conventional low-flow oxygen showing the greatest improvement.[21] However, additional research and randomised controlled trials were unable to support the initial findings. The role of remdesivir was clearly refuted in a phase 3 randomised controlled trial named DisCoVeRy. They determined that there was no therapeutic advantage to using remdesivir in patients who had been admitted to a hospital with COVID-19, were symptomatic for a duration of more than seven days, and needed oxygen assistance.[11] The WHO Solidarity Trial Consortium determined that remdesivir regimens had little or no influence on hospitalised COVID-19 patients' overall mortality, ventilation initiation, or length of hospital stay.[22] Finally, Ansems et al. discovered in a Cochrane review that remdesivir had little or no influence on all-cause mortality in hospitalised individuals for up to 28 days.[23] They were also unable to prove remdesivir's impact on clinical improvement and deterioration. As a result, the status of remdesivir remains uncertain, necessitating more studies to reach a definite verdict.

Conclusion

The NEWS 2 score was a good objective marker for clinical status assessment. CRP, IL-6, D-dimer, and serum ferritin were good markers of disease severity. These were high in severe patients and the patients who deteriorated. PCT can aid in the early detection of bacterial infections. The relevance of remdesivir in COVID-19 patient outcomes is still debated, with several studies supporting its benefits and various studies refuting them.

Source of Funding: None

Conflict of Interest: None

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ISSN: 2349-7181
DOI: https://doi.org/2010.24321/2349.7181.202216

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ISSN: 2349-7181
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