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# Association of Remdesivir with Poor Clinical Outcomes in COVID-19-A Single Center Experience

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**Abstract:** The need for an antiviral against COVID-19 prompted clinical trials worldwide and based on initial promising trends, remdesivir was widely used, including in India (compassionate use). Subsequent trials have been conflicting in their results and the utility of the drug has been widely debated. This is a record-based retrospective cohort study in a 1000-bedded government teaching hospital in North India. We reviewed the medical e-records of the COVID-19 positive patients admitted between June and November 2020. After assessing eligibility and making the necessary exclusions, 112 patients were retrospectively included in the remdesivir cohort and 85 in the standard care cohort. All the baseline characteristics of relevance and hospital admission details were collected. The following outcomes were assessed: All-cause mortality until discharge-stratified as per baseline oxygen support, age, gender, and co-morbidities; the proportion of severe and non-severe patients progressing to mechanical ventilation later on; and time to clinical recovery in survivors. We found a statistically significant association of higher mortality with the administration of remdesivir (odds ratio, OR 2.3, p-value 0.008) with a Cox regression hazard ratio of 1.590 (CI 0.944-2.679). The trend towards poorer outcomes in the remdesivir cohort persisted even after sub-stratification for age, gender, baseline severity (oxygen need), and co-morbidities but failed to reach statistical significance in most strata. Similarly, remdesivir administration was associated with higher rates of progression to mechanical ventilation amongst those severe and non-severe patients who were not on mechanical ventilation at admission (49% versus 15%, p-value <0.001, OR 5.2). This association was significant overall as well as for severe category patients when assessed separately (56% versus 26%, p-value 0.04, OR 3.1). There was, however, no difference in the days taken for clinical recovery between the two groups (13.23 days versus 12.8 days, p-value 0.77). Remdesivir administration was associated with overall worse clinical outcomes. This study contradicts the benefits shown with remdesivir in previous clinical trials done in controlled settings and highlights the challenges that newer therapies face in real-life hospital settings. There is a need to include diverse ethnic groups in the future clinical trials of the drug if to be used.

**Keywords:** Antiviral Therapy, Clinical Recovery, Coronavirus Disease, Mortality

## Introduction

Remdesivir (also known as GS-5734) is a prodrug first developed against the Ebola virus in 2017 and was identified as a potential therapy for the SARS-COV 2 based on in-vitro studies and studies in primate models (Warren *et al*., 2016; Mulangu *et al*., 2019; Wang *et al*., 2020a; Sheahan *et al*., 2017; Williamson *et al*., 2020).

This prompted clinical trials worldwide and based on the early results, the FDA issued emergency use authorization to remdesivir on 1 May 2020 (FDA, 2020).

The earliest Randomized Controlled Trial (RCT) of remdesivir in COVID-19 was conducted in China and showed numerical tendencies favoring treatment with remdesivir (Wang *et al*., 2020b). The phase 3 Adaptive COVID-19 Treatment Trial-1 (ACTT-1) demonstrated a shorter time to clinical recovery in the remdesivir arm for those on supplemental oxygen (Beigel *et al*., 2020). However, the largest RCT of remdesivir to date, the WHO-sponsored solidarity trial, did not find any reduction in overall mortality, the need for ventilation, or the duration of hospital stay (WHOSTC, 2021). Not surprisingly, there is no consensus amongst the world's leading health organizations regarding the use of remdesivir. Nevertheless, the drug was widely prescribed worldwide (compassionate use) during the pandemic, including in India. For more rational use of remdesivir, further detailed studies are the need of the hour.

In this study, we have retrospectively compared the outcomes of the patients who were administered remdesivir (out of the trial, in the real-life scenario) with those who received standard treatment alone in a tertiary care hospital in North India.

## Materials and Methods

### *Study Design and Setting*

We conducted the study at a 1000-bedded teaching hospital (tertiary level referral center) in the north Indian state of Uttarakhand. The institutional ethics committee, AIIMS, Rishikesh, approved the study (No. 218/IEC/IM/NF/2020). The data collection was done through the e-medical records on the National Informatics Centre's e-hospital portal used by the hospital.

### *Study Population and Patient Selection*

All adult COVID-19 positive patients admitted between June and November 2020 were reviewed for eligibility. COVID-19 positivity was defined as having confirmed Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) positivity for SARS-COV-2 on the nasopharyngeal swab, or clinical features and chest radiological findings highly suggestive of COVID-19 infection with no other explainable diagnosis.

All those who were administered remdesivir within a trial were excluded. We also excluded participants who had received any other experimental therapy apart from remdesivir or those who had refused to give consent to use their medical data for research purposes at the time of hospital admission. A retrospective analysis of the eligible patients' medical records was carried out. All the relevant patient parameters were collected and the patients were classified as per the WHO severity categories (Rochwerg *et al*., 2020). All the study participants were divided into two cohorts-remdesivir or standard care. Standard care comprised of isolation, hydration, nutrition, supportive pharmacotherapy as indicated (antipyretics, antiallergics, cough suppressants, antibiotics for other associated infections), corticosteroids, treatment of co-morbidities and oxygen/ventilatory support, inotropes and renal replacement as and when indicated. The remdesivir cohort comprised patients who had received remdesivir and standard care, whereas the standard care cohort comprised those who received standard care alone.

### *Study Variables and Outcomes*

We collected all the relevant baseline characteristics, including demographics, symptoms, duration of illness, pre-existing co-morbidities, and medications. Data were collected from the hospital course about the treatment given, including oxygen interface, steroids, antimicrobials, and supportive care. The baseline and follow-up laboratory parameters were also noted. Duration of hospital stay (in days) was noted as well as the duration of clinical recovery from hospitalization in survivors. Oxygen support was categorized into five strata for ease of analysis: Room air, low flow, high flow, non-invasive ventilation, and invasive mechanical ventilation. 'Low flow' oxygen systems include a nasal cannula, Hudson face masks, and non-rebreather face masks (in tachypneic patients), whereas 'high flow' systems include non-rebreather face masks in normocapnic patients and high flow nasal cannula (Hardavella *et al*., 2019).

The following outcomes were assessed:

1. All-cause mortality until discharge-stratified as per baseline oxygen support, age, gender and co-morbidities
2. The proportion of severe and non-severe patients progressing to mechanical ventilation later on
3. Time to clinical recovery in survivors

### *Statistical Analysis*

We compared the quantitative variables using the Independent t-test (as the data sets were normally distributed) between two groups. For >2 groups, Analysis Of Variance (ANOVA) was used. Qualitative variables were correlated using the Chi-Square test. Fisher exact was used when the expected frequency in any cell was <5. Relationships were assessed using Pearson or Spearman tests depending upon distribution. Multivariate regression (logistic for categorical and linear for continuous dependent variables) was used to determine the significant predictor variables.

We also did a survival analysis, retrospectively following up on patients' records from symptom onset to death. We compared the time to death in treatment cohorts using unweighted Kaplan-Meier curves and univariate and multivariate Cox regression analysis. The treatment effect was studied using unadjusted and adjusted Hazard Ratio (HR) with 95% CI.

A p-value of <0.05 was considered statistically significant. The data was entered in the Microsoft Excel spreadsheet and analysis was done using IBM Statistical Package for Social Sciences (SPSS) version 26.0 (Chicago, US).

## Results

Of the 520 patients assessed for eligibility, 45 were excluded as they had missing consent forms and 125 were already enrolled in a clinical trial. Of the remaining 350, 145 were excluded because they had received at least one of the other experimental therapies for COVID-19 (favipiravir, tocilizumab, interferon, ivermectin, hydroxychloroquine, lopinavir-ritonavir, or convalescent plasma). Data collection was started for 205 patients, but eight were subsequently excluded as they had significant missing variables in the e-records. A total of 197 patients were included in the final analysis (Fig. 1).

Of these, 146 (74%) participants were males and 51 (26%) were females. 112 (57%) patients received remdesivir during the hospital stay, whereas 85 (43%) patients received standard care alone. In the remdesivir group, the mean age was 55.8 years and 86 (77%) were males compared to the mean age of 51 years and the male population of 60 (71%) in the standard care cohort. The proportion of non-severe, severe and critical patients was 17, 50, and 33%, respectively, in the remdesivir group versus 44, 33, and 23% in the standard care group. Only three co-morbidities (diabetes mellitus, hypertension, and chronic cardiac disease) were present in a significant number of patients and hence, only these were included in the final analysis. The most common co-morbidity in both groups was hypertension followed by diabetes mellitus followed by chronic cardiac disease. Only 38 (34%) patients didn't have any co-morbidity in the remdesivir group compared to 41 (48%) in the other group. Overall, the participants in the remdesivir cohort had statistically significantly higher baseline severity, age, and co-morbidities (hypertension and diabetes mellitus) (Table 1).

106 (95%) of the 112 study participants received the 5-day course of therapy and six participants received the 10-day course. For ease of categorization, we have rounded off the duration for those who could not complete the course. 88 (79%) of the patients were started on remdesivir within the first ten days after symptom onset, whereas 23 were started at >10 days (onset of symptoms could not be ascertained for one patient). The majority of patients in both cohorts received steroids.

**Table 1:** Baseline characteristics of remdesivir and standard care cohorts

| Baseline characteristic | | Remdesivir (N = 112) | Standard care (N = 85) | P-value |
|---|---|---|---|---|
| Age (years) | Mean, median and mode | 55.8, 58 and 57 | 51, 51, 57 | 0.020 |
| | Standard deviation | 14.5 | 15.5 | |
| | Minimum and maximum | 25 and 85 | 18 and 81 | |
| | ≥65 years | 31 (27.6%) | 19 (22.4%) | 0.400 |
| | <65 years | 81 (72.4%) | 66 (77.6%) | |
| Gender | Males | 86 (77%) | 60 (71%) | 0.330 |
| | Females | 26 (23%) | 25 (29%) | |
| Pre-existing comorbidities | Chronic cardiac disease (not hypertension) | 21 (19%) | 14 (16.5%) | 0.680 |
| | Hypertension | 53 (47%) | 25 (29%) | 0.010 |
| | Diabetes mellitus | 50 (45%) | 23 (27%) | 0.010 |
| | With no co-morbidity | 38 (34%) | 41 (48%) | 0.040 |
| Oxygen support at hospitalisation | Room air | 19 (17%) | 30 (35%) | 0.001 |
| | Low flow oxygen support | 32 (28.6%) | 28 (33%) | |
| | High flow oxygen support | 34 (30%) | 8 (9.4%) | |
| | Non-invasive ventilation | 19 (17%) | 12 (14%) | |
| | Invasive mechanical ventilation | 8 (7%) | 7 (8.2%) | |
| COVID-19 severity at baseline | Non-severe | 19 (17%) | 37 (44%) | <0.001 |
| | Severe | 56 (50%) | 28 (33%) | |
| | Critical | 37 (33%) | 20 (23%) | |
| Receipt of steroids during hospitalisation | Any dose | 109 (97%) | 75 (88%) | 0.010 |
| | Pulse steroid | 13 (12%) | 8 (9%) | 0.620 |

A few patients also received high dose steroids as 'pulse' steroids (dexamethasone 40 mg OD or methylprednisolone 250-500 mg OD for 3-5 days and then tapered) when suspected to have rapid deterioration due to a 'cytokine storm'. A statistically significantly higher number of patients (109; 97%) received steroids in the remdesivir cohort (including 13 participants who received a pulse dose of steroid) compared to 75 patients (88%) in the standard care cohort (of which 8 received pulse dose too).

We found statistically significant higher odds of mortality with remdesivir compared to standard care alone (p = 0.008, Odds Ratio, OR = 2.3). However, the two groups varied significantly in terms of the baseline disease severity of the participants, with the proportion of non-severe category patients being much higher in the standard care cohort. After doing indirect standardization for baseline severity, the standardized mortality rate in the remdesivir cohort was 1.24 (much less than the OR, but still higher for the remdesivir cohort). We also assessed the association of mortality with remdesivir administration after sub stratification for age, gender, co-morbidities, and baseline oxygen support.

As depicted in Table 2, there was a definitive trend towards the association of mortality with remdesivir administration across all the sub-groups, with statistical significance reached for the elderly, females, hypertensives, and those without chronic cardiac disease. Similarly, remdesivir administration was associated with higher rates of progression to mechanical ventilation amongst those severe and non-severe patients who were not on mechanical ventilation at admission. This association was significant overall as well as for severe category patients when assessed separately. There was, however, no difference in the days taken for clinical recovery between the two groups.

A Kaplan Meier curve was constructed comparing the duration of hospital stay with events as mortality and estimated the cumulative probability of death, compared between the two cohorts. There was increased cumulative mortality in the remdesivir cohort (Fig. 2). Patients treated with remdesivir had a higher Cox regression hazard ratio, suggesting a trend toward higher mortality (HR 1.590, 95% CI 0.944-2.679, p-value 0.081).

**Table 2:** Various outcomes of remdesivir and standard care cohorts

| Outcome | | Remdesivir cohort | Standard care cohort | p-value | Odds ratio |
|---|---|---|---|---|---|
| All-cause mortality | Overall | 48 (43%) | 21 (25%) | 0.008 | 2.3 |
| | Age stratified | | | | |
| | ≥65 years | 19 (61%) | 5 (26%) | 0.020 | 4.4 |
| | <65 years | 29 (36%) | 16 (24%) | 0.130 | |
| | Gender stratified | | | | |
| | Males | 33 (38%) | 14 (23%) | 0.060 | |
| | Females | 15 (58%) | 7 (28%) | 0.030 | 3.5 |
| | Stratified as per underlying co-morbidity | | | | |
| | Diabetics | 25 (50%) | 6 (26%) | 0.060 | |
| | Non-diabetics | 23 (37%) | 15 (24%) | 0.120 | |
| | Hypertensives | 31 (58%) | 8 (32%) | 0.030 | 3.0 |
| | Non-hypertensives | 17 (29%) | 13 (22%) | 0.370 | |
| | Cardiac diseased | 6 (29%) | 4 (26%) | 1.00* | |
| | Non-cardiac diseased | 42 (46%) | 17 (24%) | 0.004 | 2.7 |
| | Stratified as per oxygen support at admission | | | | |
| | Room air | 4 (21%) | 1 (3%) | 0.13* | |
| | Low flow oxygen | 12 (38%) | 5 (18%) | 0.090 | |
| | High flow oxygen | 17 (50%) | 3 (38%) | 0.80* | |
| | Non- invasive ventilation | 10 (53%) | 5 (42%) | 0.550 | |
| | Invasive mechanical ventilation | 5 (62%) | 7 (100%) | 0.250 | |
| Progression to mechanical ventilation in those not requiring mechanical ventilation at admission | Overall | 35 (49%) | 10 (15%) | <0.001 | 5.2 |
| | Non-severe category only | 5 (28%) | 2 (5%) | 0.06* | |
| | Severe category only | 30 (56%) | 8 (26%) | 0.040 | 3.1 |
| Days to clinical recovery in survivors | | 13.23±6.5 (n = 62) | 12.8±9.8 (n = 64) | 0.77 | |

*Fisher exact used

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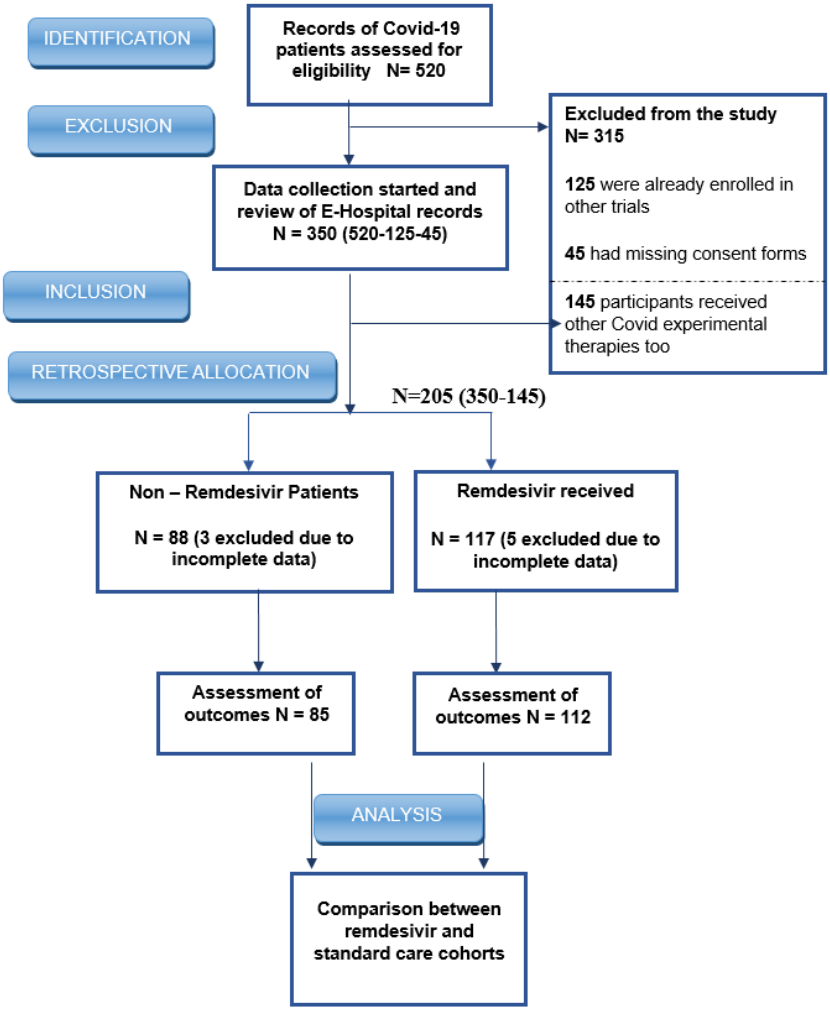


**Fig. 1:** The study flow

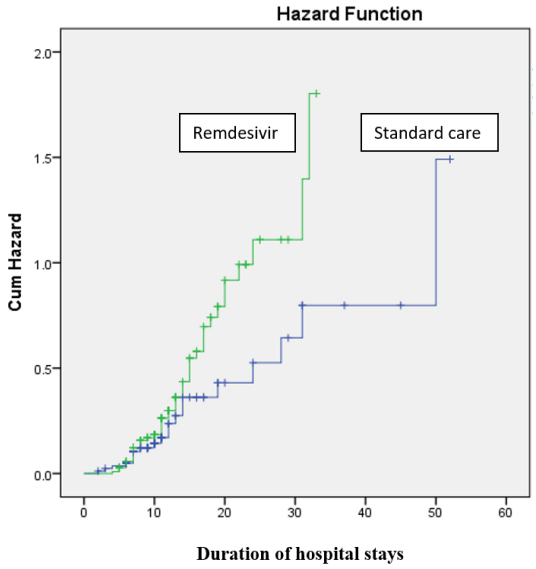


**Fig. 2:** Kaplan Meier curves of remdesivir and standard care cohorts towards cumulative mortality

## Discussion

In this retrospective analysis of medical records, we found a statistically significant association of mortality with the administration of remdesivir compared with the standard treatment alone (43% versus 25%, p-value = 0.008, Odds ratio = 2.3). The Kaplan Meier curve also showed more hazard events (death) when compared with the standard care curve (Fig. 2). As the baseline clinical severity of the two cohorts was not matched, we stratified the population as per the oxygen support required at admission. We didn't find any statistically significant difference in mortality in any group after stratification for the baseline oxygen support. This is consistent with the previous studies by Wang *et al*. (2020a) and trials like Solidarity and ACTT-1 (Wang *et al*., 2020b; Beigel *et al*., 2020; WHOSTC, 2021). However, while our study showed a trend towards higher mortality in the remdesivir cohort, the ACTT-1 showed a trend towards lower mortality with the most significant reduction in those receiving oxygen support (without any mechanical ventilation) (Beigel *et al*., 2020). The severity adjusted Standardized Mortality Rate was 1.24 times higher in the remdesivir group (close to one and much less than the crude odds ratio of 2.3). Our study also showed a trend towards higher mortality with remdesivir after stratification by age, gender, and underlying co-morbidities.

We also assessed the progression to mechanical ventilation in non-severe and severe category patients (those who were not on mechanical ventilation at admission). There was a statistically significant association with lower progression rates to mechanical ventilation in the standard care group (49% vs 15%; p-value <0.001). This finding is opposite to that seen in the Solidarity trial and meta-analyses by Kaka *et al*. (2021) and Vegivinti *et al*. (2021). As the proportion of non-severe patients was higher in our study's standard care cohort than in the remdesivir cohort, we did a subgroup analysis of progression to mechanical ventilation separately with only the non-severe and severe patients. There was no statistically significant difference (p-value 0.06) in the non-severe group but was still significant for the severe group patients (p-value 0.04). Although the study designs differed significantly, Benfield *et al*. (2021) reported reduced 30-day mortality and need for mechanical ventilation in moderate to severe Covid-19 patients treated with remdesivir plus dexamethasone compared with standard care alone (Benfield *et al*., 2021). However, in that study, the results may have been influenced by the lack of dexamethasone in the standard care cohort as well as because the remdesivir cohort comprised of patients admitted later than the standard care cohort. Olender *et al*. (2021) used patient data from a phase 3 clinical trial of remdesivir and compared these to a retrospective cohort of patients who received standard care only. They reported reduced odds of death and better 14-day recovery (Olender *et al*., 2021).

In those patients who survived till 28 days/hospital discharge (whichever was longer), we assessed the days to clinical recovery, which was only slightly higher for the remdesivir cohort when compared to standard care (13.2 days vs 12.8 days) and failed to reach clinical significance (p-value = 0.77). These findings are consistent with the Solidarity trial, whereas ACTT-1 and Wang *et al*. (2020a) reported a reduction in the time to clinical recovery with remdesivir (Wang *et al*., 2020b; Beigel *et al*., 2020; WHOSTC, 2021). While the study by Wang *et al*. (2020a) was limited by its small sample size, the ACTT-1 trial excluded patients expected to be discharged within 72 h. Hence, it is difficult to extrapolate the results of the ACTT-1 in routine practice, as has been pointed out by many researchers (Anderson *et al*., 2021). Garibaldi *et al*. (2021) also reported a faster clinical improvement in a cohort of predominantly non-white patients. In a large retrospective cohort study done on 2344 US veterans, the duration of hospital stay was significantly higher for the remdesivir cohort (3 days vs 6 days) when compared with matched controls (Ohl *et al*., 2021). For a drug with no mortality benefit, prolonged hospital stays would mean the wastage of the precious hospital beds during the pandemic. The most likely explanation is that the clinicians may not have discharged the patients even after clinical improvement, just to complete the course of remdesivir. In an RCT by Mahajan and AP Singh (2021) from North India, they found similar mortality and recovery times between remdesivir and standard care arms, thus shedding light on the importance of regional/ethnic variations in study outcomes (Mahajan and AP Singh, 2021).

The explanation for the poor outcomes seen with remdesivir may also lie in the retrospective nature of our study. Since we have only included those participants who were administered remdesivir outside of any clinical trial (compassionate use), it is reasonable to assume that any experimental drug would only be used by the treating physician in the setting of worsening clinical condition, especially when the supply is scarce and the drug is expensive. Although we did stratify the patients as per the baseline oxygen support, the true clinical condition is dictated by much more than merely the oxygen support. The impact of remdesivir is likely to depend on several other variables also, like absolute neutrophil/ lymphocyte and platelet counts, as noted in the post hoc analysis of ACTT-1 by Paules *et al*. (2021). Hence, it is reasonable to assume that the unadjusted confounders may have affected the results as in all observational studies.

### *Limitations*

Our study had many limitations. Firstly, the sample size was small and uneven in both cohorts, leaving little scope for meaningful stratification. Many observations were made and trends noted in our present study that would have required larger sample sizes to reach statistical significance. Secondly, ours was a retrospective study and the two cohorts were not matched for baseline characteristics. Thirdly, our case records did not document many parameters like respiratory rate, the

precise fraction of inspired $O_2$ ($FiO_2$), patient position, follow-up investigations, adverse drug reactions, etc. Hence, these could not be included in the analysis. Lastly, there was no follow-up of patients.

## Conclusion

In real-life hospital setting amid a pandemic in a developing nation, the study highlights the challenges that newer therapies face. Remdesivir administration was associated with overall worse clinical outcomes against COVID-19. It had emerged as a promising tool in the studies done in the developed countries (ACTT-1) but was found to make no difference to outcomes in a more global trial (the Solidarity trial). It highlights that a clinical trial's (controlled setting) results may not be entirely reproducible in a real-life setting.

### *Data Sharing*

It will be made available to others as required upon requesting the corresponding author.

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## Author's Contributions

**Rajat Ranka:** Did literature search, collected data, drafted the manuscript and approved.

**Arjun, Yogesh Arvind Bahurupi and Disha Agarwal:** Did a literature search, analyzed data, reviewed the manuscript and approved.

**Prasan Kumar Panda and Gaurav Chikara:** Gave concept and design, interpreted data, reviewed critically the manuscript and approved.

## Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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