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Coronavirus Pandemic

Outcome of COVID-19 and tolerance of Remdesivir in patients with renal failure: a single center experience from Pakistan

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Abstract

Introduction: Coronavirus disease-19 (COVID-19) is known to cause severe disease in chronic kidney disease and maintenance dialysis patients. We aim to report the outcome of COVID-19 and the adverse effects of Remdesivir (RDV) in patients with renal failure.

Methodology: A retrospective observational study included all admitted patients with COVID-19 who received Remdesivir. Clinical characteristics and outcomes were compared in patients with renal failure (RF) and non-renal failure (NRF). We also evaluated RDV-associated nephrotoxicity and observed renal functions during antiviral treatment.

Results: A total of 142 patients received RDV, 38 (26.76%) in RF and 104 (73.23%) in the non-RF group. The median absolute lymphocyte count was low while C-reactive protein, ferritin, and D-dimer were significantly high on admission in the RF group. A significant number of patients in the RF group required ICU admission (58% vs. 35% $p = 0.01$) and expired (29% vs. 12.5 $p = 0.02$). Among survivors and non-survivors in the RF group, raised inflammatory markers and low platelet count on presentation were significantly associated with high mortality. Median serum creatinine (mg/dL) was 0.88 on admission, remained at 0.85 in the NRF group, and improved from 4.59 to 3.87 (mg/dL) after receiving five days of RDV in the RF group.

Conclusions: COVID-19 in renal failure has a high risk for ICU admissions leading to increased mortality. Multiple comorbidities and raised inflammatory markers are predictors of poor outcomes. We observed no significant drug-related adverse effects, and none of our patients required discontinuation of RDV due to worsening renal function.

Key words: COVID-19, renal failure, remdesivir, mortality.

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Introduction

The Coronavirus disease-19 (COVID-19) pandemic due to Severe Acute Respiratory Syndrome Corona Virus -2 (SARS-CoV-2) has resulted in severe strain on public healthcare systems across the globe. Among other comorbidities, patients with renal failure infected with SARS-CoV-2 have very high mortality (around 25-40%), prompting the need for effective treatment options [1–3]. Antiviral agent Remdesivir (RDV) is an inhibitor of viral RNA-dependent RNA polymerase and has in-vitro activity against all coronaviruses, including SARS-CoV-2 [4]. Several randomized trials on the use of RDV have been published. A randomized controlled trial from China and then from the United States (ACTT-1) showed a faster time to clinical improvement in RDV compared to the placebo or standard of care group [5,6]. However, World Health Organization (WHO) sponsored a trial on COVID-19 treatment; the largest trial to date showed no difference in the overall mortality [7]. Since then, RDV has been adopted in the COVID-19 treatment guidelines worldwide with the indication to use among patients with mild to moderate COVID-19 [8]. In a retrospective study, Garcia-Vidal *et al.* found a low mortality rate in patients who received RDV early in their disease course [9].

However, in almost all the trials, patients with severe renal failure were excluded. This is due to concerns regarding the accumulation of its excipient sulfobutylether-b-cyclodextrin (SBECD), which may cause renal and hepatic toxicity. Plasma t½ of its active metabolite is 20-25 hours with widespread tissue distribution [10]. Hence, the potential benefit of RDV is prevented due to limited data availability in patients with renal failure. Assessing drug-induced nephrotoxicity in patients with COVID is challenging as the disease bears renal complications. Although two major randomized controlled trials (RCTs) showed no significant adverse events in terms of deranged renal

and liver function tests in the RDV group, RDV is still not indicated in patients with an eGFR < 30 mL/min due to underrepresentation of participants in RCTs [5,6].

Thakre *et al.* reported no significant renal impairment with RDV in patients with acute kidney injury (AKI) or chronic kidney disease (CKD). However, the numbers were few, and no controls for comparison [11]. A single-center comparative study on patients with severe renal impairment found no statistically significant elevation in serum creatinine after RDV administration [12]. Another retrospective observational study from Italy included 109 elderly individuals with or without CKD who showed no signs of renal dysfunction. Rather improvement in eGFR was observed [13].

Since then, guidelines worldwide have recommended its use, especially in patients with compromised renal functions. In Pakistan, the national guidelines recommend using RDV in patients requiring supplemental oxygen [14]. Data on the outcome of COVID-19 patients with renal failure and the use of RDV in this population is limited from Pakistan. Yaqub *et al.* reported AKI as an independent risk factor for mortality [15]. Another study reported high mortality among hemodialysis patients with older age and high inflammatory markers as predictors of mortality [16]. This study aims to evaluate the treatment outcome of COVID-19 and nephrotoxicity of RDV in patients with renal failure.

Methodology

A retrospective observational study was performed at the Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan. SIUT is the largest transplant center in Pakistan. It caters to a large dialysis unit and patients with urological and renal diseases.

All patients aged ≥ 18 years with confirmed SARS-CoV 2 Polymerase Chain reaction (PCR) positive, admitted from June 2020 to March 2021, and received RDV were included. RDV was given as 200 mg on day one, followed by 100 mg daily for four days. Other drugs for COVID-19, like corticosteroids and tocilizumab, were given as per national guidelines. Our hospital protocol allowed cautious use of RDV in patients with low estimated glomerular filtration rate (eGFR) and deranged liver functions. Transplant recipients were excluded from the study. Patients were divided into renal failure (RF) and non-renal failure groups (NRF). RF can be acute kidney injury (AKI) or chronic kidney disease (CKD), as defined below.

A detailed chart review was done to extract baseline characteristics, clinical features, degree of hypoxia, and laboratory parameters, including inflammatory markers like C-reactive protein (CRP), ferritin, and lactic dehydrogenase (LDH) at presentation. In addition, information on treatment with Remdesivir, use of steroids or tocilizumab, need for ICU admission, and invasive mechanical ventilation was gathered. These variables were compared into RF and NRF groups. The primary endpoint was mortality at day 28 and adverse effects of RDV. Variables associated with 28 days of mortality, including age, gender, coexisting medical conditions, laboratory parameters, and treatment, were compared between survivors and non-survivors in the RF group. Clinical assessment by using a 6-point ordinal scale during hospital stay was noticed. For adverse effects of Remdesivir, serum creatinine was noted at days 0, 5, and 7 days after RDV administration.

This study received approval from the Ethical Review Committee of the hospital.

Operational definitions

World Health Organization 6-point ordinal scale of clinical status

The 6-point ordinal scale is as follows: 1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring high flow nasal cannula, non-invasive mechanical ventilation, or both; 5, hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 6, death [17].

Acute Kidney Injury

Acute Kidney Injury is defined as any of the following: An increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours; or an increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days; or urine volume < 0.5 mL/kg/h for 6 hours [18].

Chronic Kidney Disease

Kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for at least three months. There are 5 Stages of CKD [19].

Statistical analysis

SPSS version 20 was used to analyze the data. Continuous variables were reported as mean ± SD and categorical variables were presented as frequencies and percentages. To compare the mean difference between groups for continuous variables two-sample t-test was used, whereas the chi-square independent test or Fisher exact test was used to determine the proportion

difference between groups. A p value < 0.05 was considered significant for categorical variables.

Results

A total of 142 SARS-CoV-2 positive patients received RDV. The mean age was 56 ± 14 years, and 65.49% were male. Thirty-eight (26.76%) were in the RF group, and 104 (73.23%) were in the NRF group.

Table 1 shows the baseline characteristics and the comparison between RF and non-RF groups.

Mean age and gender were comparable. Overall, the RF group had significantly more comorbidities as compared to the non-RF group [84.2% vs. 60.6% p = 0.008 95% CI 3.47 (1.33-9.03)], among which hypertension was most significant [68% vs 31% p < 0.001, 95% CI 4.87 (2.19-10.85)]. There was no difference in clinical manifestations in both groups. In laboratory parameters, patients in the RF group had high CRP (12.50 vs. 7.62 p= 0.007), ferritin (1180 vs. 431 p < 0.001), and D-dimers (2.52 vs. 0.64 p < 0.001) at the time of presentation.

On admission, significantly more patients in the RF group were in WHO category-3, i.e., on supplemental oxygen [63.2% vs. 39.4% p = 0.012 95% CI 2.634 (1.223 – 5.675)] and in category-5, i.e., requiring mechanical ventilation [13.2% vs. 1.9% p = 0.015 95% CI 7.727 (1.431 – 41.717)].

Regarding treatment, there was no difference among both groups who received tocilizumab, steroids, or anticoagulants. However, significantly more patients in the RF group received antibiotics due to concomitant bacterial infection.

A significant number of patients in RF required ICU admission [57.9% vs. 34.6% p = 0.012 95% CI 2.60 (1.21-5.55)] and died at day 28 [28.9% vs. 12.5 p = 0.021 95% CI 2.85 (1.15-7.09)].

Table 2 shows variables associated with 28 days of mortality in the RF group. ICU admission was the only significant risk factor for mortality [91% vs 44% p = 0.012 95% CI 12.500 (1.397-111.836)].

Serum creatinine during remdesivir treatment was compared among RF and NRF groups. The median serum creatinine (mg/dl) was 0.88 on admission and remained at 0.94 in the NRF group, while median creatinine improved from 4.59 to 3.87 on day seven after getting RDV in the RF group (Figure 1).

Table 1. Baseline characteristics of the study population.

	Overall (n = 142)	Renal disease (n = 38)	Non renal disease (n = 104)	*p* value	OR (95% CI)
Age mean (± S.D.)	55.93 ± 14.36	54.34 ± 12.61	56.51 ± 14.99	0.190	-
Age groups *n* (%)					
< 45 years	30 (21.12)	8 (21.10)	22 (21.20)	0.990	0.994 (0.40-2.47)
> 45 years	112 (78.87)	30 (78.9)	82 (78.8)		
Gender *n* (%)					
Male	93 (65.49)	24 (63.2)	69 (66.3)	0.723	0.87 (0.40-1.88)
Comorbidities *n* (%)	102(71.83)	32 (84.2)	63 (60.6)	< 0.008	3.47 (1.33-9.03)
Diabetes mellitus	57 (40.14)	20 (52.6)	37 (35.6)	0.066	2.01 (0.95-4.27)
Hypertension	58 (40.84)	26 (68.4)	32 (30.8)	< 0.001	4.87 (2.19-10.85)
Ischemic heart disease	20 (14.08)	6 (15.8)	14 (13.5)	0.724	1.20 (0.43-3.40)
Symptoms *n* (%)					
Fever	121 (85.2)	30 (78.9)	91 (87.5)	0.204	0.54 (0.20-1.42)
Cough	85 (59.85)	21 (55.3)	64 (61.5)	0.499	0.77 (0.36-1.64)
Myalgia	35 (24.64)	4 (10.5)	31 (29.8)	0.018	0.28 (0.09-0.85)
Difficulty in breathing	74 (52.11)	20 (52.6)	54 (51.9)	0.940	1.03 (0.49-2.17)
Diarrhea	12 (8.45)	5 (13.2)	7 (6.7)	0.223	2.10 (0.62-7.07)
Laboratory parameters on admission, median (IQR)					
Absolute lymphocyte count (ALC)	1058 (670-1401)	919 (544-1372)	1113 (724-1407)	0.139	-
LDH	384 (304-556)	387 (312-606)	384 (300.5-551)	0.415	-
CRP	8.93 (3.39-13.95)	12.50 (8.37-21.40)	7.62 (3.09-12.30)	0.007	-
Ferritin	610 (312-1122.4)	1180 (626-3154)	431 (278.8-806.5)	< 0.001	-
SGPT	40 (27-55)	33 (21.50-44.50)	44.0 (30-61)	0.039	-
D-dimer	0.84 (0.55-2.28)	2.52 (1.80-7.85)	0.64 (0.45-1.0)	< 0.001	-
Treatment *n* (%)					
Antibiotics	61 (42.95)	27 (71.7)	34 (32.7)	< 0.001	5.05 (2.24-11.38)
Steroids	128 (90.14)	36 (94.7)	92 (88.5)	0.267	2.35 (0.50-11.01)
Tocilizumab	38 (26.76)	7 (18.4)	31 (29.8)	0.175	0.53 (0.21-1.34)
Anticoagulation	115 (80.9)	30 (78.9)	85 (81.7)	0.708	0.84 (0.33-2.11)
ICU admission	58 (40.84)	22 (57.9)	36 (34.6)	0.012	2.60 (1.21-5.55)
Mortality at day 28	24 (16.90)	11 (28.9)	13 (12.5)	0.021	2.85 (1.15-7.09)

Figure 1. Serum median creatinine (mg/dl) in renal failure and non-renal failure groups.

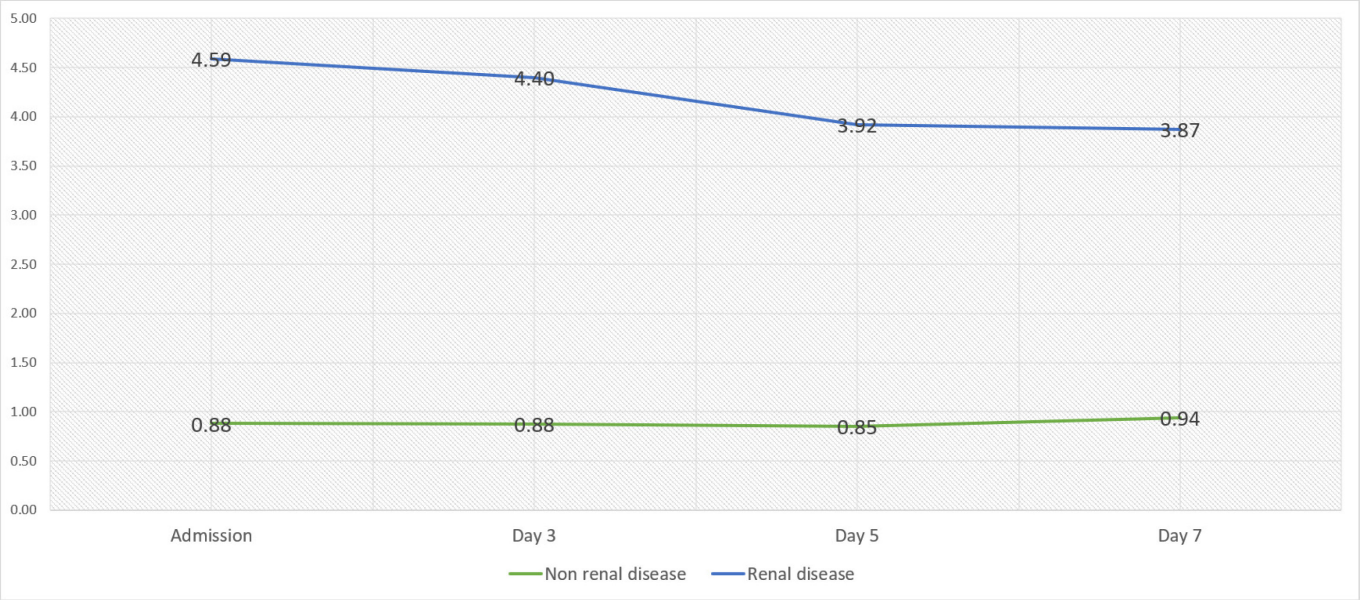


Table 2. Risk factors of mortality in renal failure patients.

	Expired (n = 11)	Alive (n = 27)	*p* value	OR (95% CI)
Age mean (± S.D)	54.73 ± 10.01	54.19 ± 13.71	0.448	-
Age group n (%)				
≤ 45 years	1 (10)	7 (25)	0.318	0.33 (0.04-3.12)
> 45 years	9 (90)	21 (75)		
Gender				
Male	7 (70)	17 (60.70)	0.601	1.51 (0.32-7.12)
Comorbid condition n (%)				
Diabetes mellitus	6 (60)	14 (50)	0.587	1.50 (0.35-6.49)
Hypertension	8 (80)	18 (64.3)	0.359	2.22 (0.39-12.55)
Ischemic heart disease	1 (10)	5 (17.9)	0.559	0.511 (0.052-5.00)
Laboratory parameters, median (IQR)				
Absolute lymphocyte count	996 (545-1398)	919.50 (535-1340)	0.896	-
LDH	378 (259-603)	389 (321-628)	0.505	-
C-reactive protein	13.07 (10.55-20.63)	11.5 (6.65-21.53)	0.622	-
Ferritin	2168 (1281-3159)	954 (610-3952)	0.208	-
SGPT	41.50 (26.25-237.50)	28.50 (15.0-39.25)	0.090	-
D-Dimer	5.65 (1.21-8.88)	2.28 (1.80-5.31)	0.628	-
Treatment given n (%)				
Steroid	10 (90.9)	26 (92.9)	0.470	0.345 (0.020-6.042)
Tocilizumab	3 (27.3)	4 (14.8)	0.390	2.156 (0.394-11.790)
Anticoagulation	8(72.7)	22 (81.5)	0.667	0.606 (0.117-3.138)
Antibiotics	10 (90.9)	17 (62.9)	0.124	5.882 (0.652-53.032)
ICU admission	10 (90.9)	12 (44.4)	0.012	12.50 (1.397-111.836)

In the RF group, 63% of patients were on oxygen and 13% on mechanical ventilation at admission. On day 14, 3% were on oxygen, 3 % on non-invasive ventilation, and 63% were discharged home.

In contrast, in the NRF group, 39% were on oxygen and 2% on mechanical ventilation at admission, while on day 14, 5% were on oxygen, 1 % on MV, and 83% were discharged home (Figure 2).

Discussion

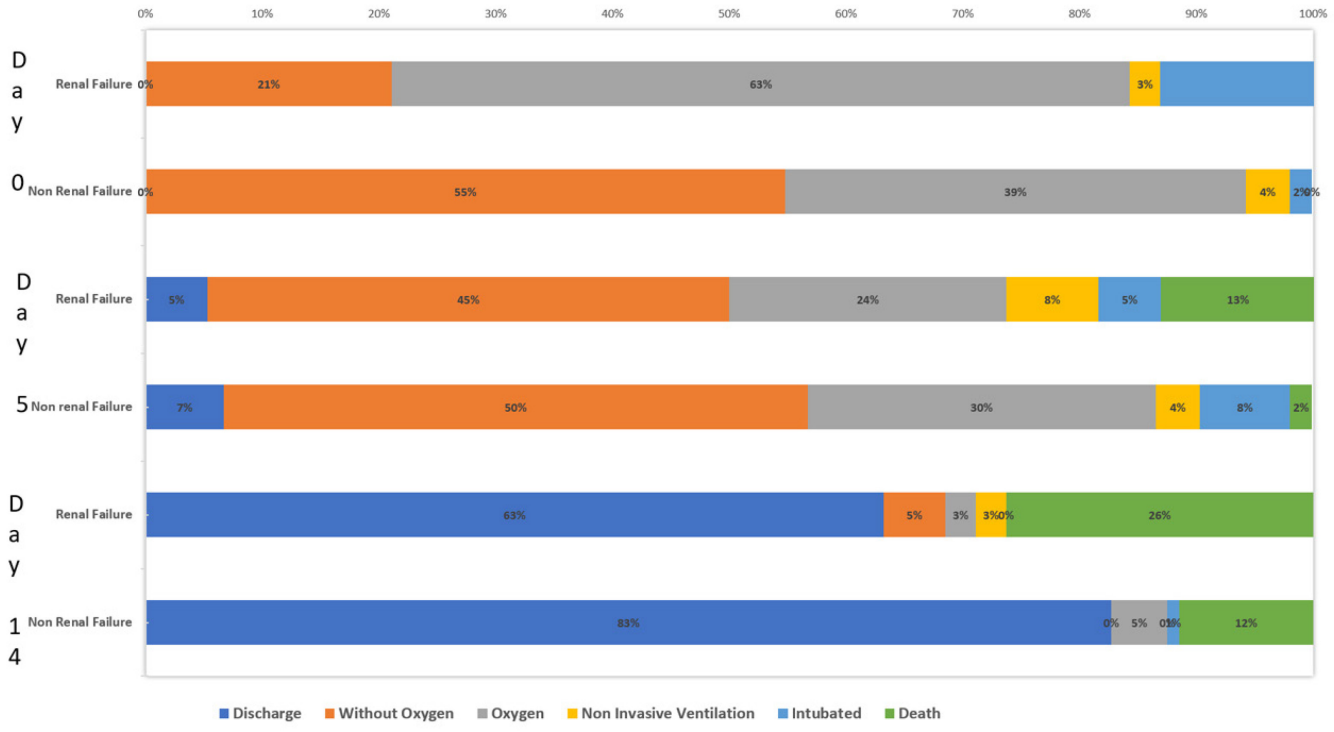
In this study, we described the outcome in terms of mortality and adverse effects of RDV in patients with compromised renal functions. To the best of our knowledge, this is the first study at a national level to evaluate nephrotoxicity associated with RDV.

RF patients are more prone to develop COVID-19 because of relative immunocompromised status, concomitant comorbidities, frequent hospital visits for dialysis, and limited ability to isolate [20].

In this study, we found that patients with RF had significantly raised inflammatory markers at presentation, mainly because significantly more patients in this group presented with severe disease (hypoxia or needing a mechanical ventilator). Oyelade *et al.* did a systematic review of 22 studies and found that the severity of COVID-19 was 83% among patients with underlying CKD. They defined severity as the length of hospital stay, ICU admission, or on mechanical ventilation [21]. We also found in our study that in the RF group, a significant number of patients got admitted to ICU, and more than 40% had prolonged hospital stays of > 14 days. Dysregulated immune system, associated comorbidities like hypertension, and one major organ dysfunction may lead these patients to have severe COVID-19 infection leading to ICU and prolonged hospital stay.

We found that the fatality rate is much higher among patients with RF. Of note, we took all severe COVID-19 patients who required hospitalization and found a high death rate in RF (28.9%) and NRF groups (12.5%) compared to the general population. These findings are in concordance with previous studies. Rastad *et al*., in a retrospective cohort study, observed high in-hospital mortality of patients with end-stage renal disease compared to the general population [22]. Another study from the USA in critically ill patients reported that preexisting kidney disease presents with severe COVID-19 and carries a significantly high mortality [23]. RF patients with COVID-19 have a higher incidence of cardiac complications, thromboembolism, and bacterial infections; therefore, it is not surprising to see increased mortality rates in this population [12,13,22].

Figure 2. Six Point Ordinal Scale in renal and non-renal failure groups.



Although we did not find a statistical difference in risk factors associated with mortality, more patients in the non-survivor group had advanced age, concomitant hypertension, and laboratory evidence indicating the presence of a cytokine storm (raised CRP, ferritin, and D-dimer). In our study, ICU admission was the only significant risk factor for mortality. Our findings are consistent with studies from China and Turkey, where advanced age, comorbidities, and high inflammatory markers were the risk factors for mortality among renal failure patients [22,24].

No significant drug (RDV) related liver function abnormalities were seen in our cohort of patients except in one patient. However, it might not be attributable to a drug, as COVID-19 can cause liver enzyme elevations. We evaluated RDV-associated nephrotoxicity, and our findings suggest that it is very well tolerated even in patients with reduced renal functions. None of our patients developed end-of-treatment AKI. Serum creatinine in RF patients showed improvement in renal functions during RDV administration. Biancalana *et al.* also observed an improvement in eGFR after RDV administration in elderly patients with COVID-19 pneumonia [13]. The higher mortality of COVID-19 with AKI and CKD indicates greater urgency to use RDV to reduce complications. RDV-associated nephrotoxicity should only prevent its use if the evidence of additional toxicity is a more compelling threat to the patient's morbidity and mortality than COVID-19 itself. The main strength of our study is that it is the only study from Pakistan that evaluates the tolerance of RDV in renal failure patients with serial monitoring of serum creatinine during treatment. Our analysis has several limitations, including the observational study design, therapeutic drug levels were not monitored in patients with decreased renal functions, and the efficacy of Remdesivir in renal failure patients could not be compared head-to-head as all patients received RDV.

In conclusion, we found that renal failure patients had higher in-hospital mortality as compared to non-renal failure patients. Although Remdesivir was well tolerated, as our study provides evidence that the adverse effects of Remdesivir were negligible, there was an improvement in renal functions. Therefore, RDV can be used safely in renal failure patients with COVID-19 pneumonia. Hence, higher mortality of COVID-19 with AKI and CKD indicates greater urgency to use RDV in this patient cohort.

Authors' contributions

Zaheer Udin Babar contributed to the study conceptualization, data collection, and manuscript writing. Sunil Kumar Dodani contributed to the study methodology, data analysis, and interpretation. Jawahar Lal and Sanjay Kumar participated in the designing methods, created figures, and revised the manuscript. Asma Nasim contributed to the study conceptualization and data interpretation and critically reviewed the manuscript.

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