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AN OBSERVATIONAL STUDY OF THE USE OF REMDESIVIR IN MODERATE COVID-19 PNEUMONIA IN PATIENTS WITH END STAGE RENAL FAILURE AT A TERTIARY COVID CARE HOSPITAL

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ABSTRACT

Background: Patients with end-stage renal disease (ESRD) on maintenance haemodialysis are more prone to the development of severe coronavirus disease 2019 (COVID-19) infection. Use of remdesivir was associated with survival benefit in severe COVID-19 patients with ESRD.

Aim: The present study evaluated the clinical experience of compassionate outcome and safety profile of remdesivir in patients with end-stage renal disease and moderate to severe COVID-19 infection.

Methods: An observational prospective study was conducted in dialysis-dependent patients with COVID-19 infection who received remdesivir as a treatment regimen. Demographic data, state of illness, medical history, laboratory tests, therapeutic intervention, total leucocyte, neutrophils, and lymphocytes, serum concentrations of erythrocyte sedimentation rate, C-reactive protein, ferritin, interleukin-6 level, lactate dehydrogenase, aspartate and alanine transaminases, and D-dimer, and outcome of patients were collected. As per the national guidelines for community-acquired pneumonia patients were classified into mild, moderate, and severe cases. A dose of 100 mg of remdesivir was administered in each patient. Data were analyzed using independent sample t-test, Mann-Whitney U test, chi-square, and Kaplan-Meier survival and mortality test.

Results: Out of 38 patients (mean age, 57.4 years), 3 (7.9%), 9 (23.7%), and 26 (68.4%) patients had mild, moderate, and severe COVID-19 infection, respectively. Hypertension (100.0%), type-2 diabetes mellitus (65.8%), and hepatitis C virus (2.6%) were common comorbid conditions. Lymphocyte count was significantly lower in those patients with severe disease (7.8 vs. 12.5 x 109/L; P=0.036). Eleven patients with severe COVID-19 infection required mechanical ventilation support. Higher lactic dehydrogenase levels were found in patients who died compared to in patients who discharged (850.0 vs. 593.0 U/L; P=0.017). The post-treatment laboratory parameters were within acceptable limits. No patient reported any immediate adverse effects after infusion of remdesivir.

Conclusion: Remdesivir was well tolerated and it may be considered as a therapeutic option in the treatment of ESRD patients on maintenance haemodialysis with COVID-19 infection.

KEYWORDS : Kidney disease, end-stage renal disease, corona, haemodialysis

INTRODUCTION:

The global outbreak of Coronavirus Disease 2019 (COVID-19) has produced a protracted medical, social, and economic crisis all over the world. Several prognostic factors for COVID-19 have been reported from previous studies [1]. End-stage renal disease (ESRD) is key risk factors for serious health issues. Some clinical studies have previously evaluated that these disorders are more susceptible to the development of severe COVID-19 which is associated with high mortality in COVID-19 patients [2-3].

Treatment of COVID-19 among patients on maintenance haemodialysis (HD) requires special pharmacotherapy considerations. Several antimicrobial and anti-inflammatory/ adjuvant drugs are being used under clinical trial for the treatment of COVID-19 [4]. Although hydroxychloroquine plus tacrolimus are significantly associated with a reduction in viral load in a kidney transplant patient however post-treatment data revealed that this combination was associated with adverse drug-drug interaction effects [5]. Currently published retrospective study reported no clinical benefit of tocilizumab in terms of mortality rate or need for mechanical ventilation. In addition, all patients had increased IL-6, CRP, D-dimer, ferritin, or lactic acid dehydrogenase or rapidly progressive acute respiratory distress syndrome (ARDS) [6].

The incidence of COVID-19 has been rising and researchers are grappling to find an effective therapy. To date, no clear guidelines exist for the management of COVID-19 in renal patients. Recently, compassionate use of remdesivir has provided some clinical improvement in patients with COVID-19 patients [7]. Moreover, an interim analysis of the Adaptive COVID-19 Treatment Trial supports the clinical efficacy of remdesivir, compared to control. Interestingly, a faster recovery time was observed post remdesivir treatment [8]. Based on these initial findings, the U.S. Food and Drug Administration has issued an Emergency Use Authorization for use of remdesivir for the treatment of hospitalized COVID-19 patients [9].

Indian studies evaluating the clinical effectiveness and tolerability of remdesivir in patients with COVID-19 on

maintenance dialysis are scarce [10,11] and there is a need to establish a better efficacy and safety profile of remdesivir in COVID-19 on maintenance dialysis. Therefore, the present prospective study aimed to assess the clinical experience of remdesivir use in the treatment of patients with COVID-19 on maintenance.

MATERIALS AND METHODS:

Study design and participant criteria

This prospective observational study was conducted at the Department of Nephrology, Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai, Maharashtra, India. Patients with kidney disease were identified based on the World Health Organisation (WHO) interim guidance and enrolled in this study. Written informed consent was obtained from all the patients. All patients with ESRD requiring HD who tested positive for COVID-19 infection and who received a dose of remdesivir were included in this study. Patients with chronic liver disease or patient with chronic kidney disease (CKD) who were not on maintenance dialysis were excluded from this study.

Data collection

Computed tomography (CT) or nasal or throat swab specimens were obtained from all patients upon admission. COVID-19 was diagnosed by clinical manifestations, computed tomography (CT) scan of the lungs, or real-time polymerase chain reaction assay according to WHO interim guidance [12]. Clinical report forms of all the study patients were obtained from electronic medical records to obtain demographic data (age, sex, and comorbidities), state of illness, medical history, laboratory tests, therapeutic intervention, and outcome data were obtained and evaluated. Blood parameters including the counts of total leucocyte, neutrophils, and lymphocytes, serum concentrations of Erythrocyte Sedimentation Rate (ESR), C-reactive protein, ferritin, interleukin-6 level (IL-6), lactate dehydrogenase (LDH), aspartate and alanine transaminases (AST, ALT), and D-dimer of patients were collected. The data collection forms were reviewed independently by experienced physicians.

Severity of COVID-19

As per the national guidelines for community-acquired pneumonia and the diagnosis and treatment plan for the new coronavirus in India all patients were classified into non-severe or severe cases based on observations from chest radiography, clinical examination, and symptoms. Patients with no clinical signs and symptoms (asymptomatic) and patients with mild symptoms (such as fever, cough, sore throat, headache, nasal congestion) and uncomplicated upper respiratory tract infection were classified as non-severe type. Patients with suspected respiratory infection symptoms or fever plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO2 ≤93% on room air were classified as severe type [12].

Treatment regimen

The conservative medical treatment consisted of a combination of a corticosteroid (methylprednisolone), anti-parasite (ivermectin), and antibiotic (azithromycin). Anticoagulant therapy (heparin/ aspirin) was administered in moderate to severe cases depending upon the condition of patient. Antiviral therapy of remdesivir was administered in mild to severe patients. Remdesivir was given within 10 days of symptom onset in COVID positive patients. A dose of 100 mg of remdesivir was administered instead of a loading dose of 200 mg. After 4 hours of administration, patients were given 4-h sessions of HD. Remdesivir was given only to those patients without any baseline liver disorder and those who gave written consent before starting the therapy. Patients were assigned to 5 doses of 100 mg intravenous remdesivir given on alternate days. In case of severe respiratory failure patients requiring non-invasive or invasive ventilation, tocilizumab 400 for two days was administered.

Statistical analysis

Data were analysed using Statistical Package for The Social Sciences (SPSS) software, version 22.0. Qualitative data were presented as numbers and percentages, while quantitative data were presented as mean (standard deviation [SD]) or median (range), depending on the normal or skewed distribution of data. The normal distribution of quantitative data was assessed by the Shapiro-Wilk test. The independent sample t-test or the Mann-Whitney U test was used for the continuous variables and the chi-square test for the categorical variables. The Kaplan-Meier plots were used to analyse time-to-event outcomes (clinical improvement and mortality). A $P<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 38 patients with COVID-19 were included in the study. The mean age of the study population was 57.4 years. The proportion of male patients was higher than female patients (65.8% vs 34.2%). The vascular access for HD included internal jugular vein central venous in 50.0% of patients, arteriovenous fistula in 35.0%, and permacath in 15.0%. The main coexisting conditions were hypertension (HTN) (100.0%), type-2 diabetes mellitus (T2DM) (65.8%), and hepatitis C virus (2.6%). Twenty-one patients (55.3%) were being treated with renal replacement therapies. Out of 38 patients, 3 (7.9%) and 9 (23.7%) patients had mild and moderate COVID-19 infection, respectively, while 26 (68.4%) had severe COVID-19 infection [Table 1].

Laboratory Characteristics

Results of baseline laboratory tests are summarized in table 1. Patients showed elevated median levels of neutrophil count (83.2 x 10^9/L), lymphocyte count (8.5 x 10^9/L), ESR (63 mm/h), CRP (87.0 mg/dL), ferritin (1.4 mg/mL), IL-6 (22.3 pg/mL), lactic dehydrogenase (665.0 U/L), and D-dimer (2.2 g/mL) at the time of admission. The median total leucocyte count, AST and ALT levels were in the normal range (11.7 x 10^9 cells/L, 37.5 and 29.0 IU/L, respectively).

Clinical course of treatment

The average CT severity score was 13.3. At the time of admission (baseline), the majority (31.6%) of patients were on a high flow nasal cannula, followed by other types of oxygen therapies including mechanical ventilation (28.9%), non-invasive ventilation (23.7%), low-flow oxygen (15.8%). All patients received a combination of remdesivir with an anticoagulant regimen of heparin and a corticosteroid regimen of methylprednisolone. The most commonly used antiparasitic agent was ivermectin (97.4%). A total of three patients received tocilizumab. Total 89.5%of patients received azithromycin as an antibiotic regimen [Table 1].

Outcomes

Total of 63.2% (n = 24) of patients discharged post remdesivir treatment; while 36.8% (n =14) of patients died. The mean length of hospital stay was 14.9 days [Table 1].

Remdesivir and clinical severity

The median age was comparatively lower in patients with severe COVID-19 infection compared to those with moderate COVID-19 infection (54.5 vs. 63.9 years; P = 0.055). The prevalence of diabetes was higher in the non-severe patients than severe COVID-19 patients (75.0% vs. 61.5%; P = 0.416). The necessity for RRT was comparable in both groups (57.7% and 50.0%). Total leucocyte count, neutrophil count, ESR, C-reactive protein, ferritin, interleukin-6 level, lactic dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and D-dimer levels were comparable in

both groups. Lymphocyte count was significantly lower in those patients with severe disease (7.8 vs. 12.5 x 10^9/L; P = 0.036). The average CT severity score was slightly higher in severe patients than severe patients (13.8 vs. 12.1). Total eleven patients (42.3%) with severe COVID-19 disease required mechanical ventilation support in the total study population. The use of heparin, methylprednisolone, remdesivir, ivermectin, azithromycin, and aspirin were similar in patients from severe and non-severe groups of COVID-19 infection. However, the use of tocilizumab was more common in patients with severe COVID-19 infection. A total of 14patients had in-hospital death due to severe COVID-19 infection; while none of the patients with moderate COVID-19 infection reported in-hospital death. The mean hospital stay was comparable between both groups (15.3 and 14.7 days) [Table 2].

Discharged and death

The mean age of the patient was comparable in both patients who improved and those who died (57.8 and 56.8 years, respectively). Patients who died had severe COVID-19 infection with women predominance. Significantly higher lactic dehydrogenase levels (median (range): 850.0 (566.0-1590.0) vs. 593.0 (400.0-1430.0) U/L; P =0.017) was found in patients who died vs, those discharged. All other parameters were comparable between patients who died and survived. Patients who died were more likely to receive invasive mechanical ventilation [Table 3].

Efficacy and safety of remdesivir

The post-treatment laboratory parameters with remdesivir therapy were within acceptable limits which were consistent in the study population among various subgroups, based on age, and disease severity. No patient in the present cohort reported any immediate adverse effects after infusion of remdesivir.

Clinical improvement and mortality

The mean (95% CI) time to clinical improvement was 19.1 (16.4-21.8) days [Figure 1A] and the mean (95% CI) time to death was 21.9 (17.9-26.0) days [Figure 1B].

Table 1. Demographic characteristics

Parameters	Number of patients (N = 38)*
Age [years], mean (SD)	57.4 (14.2)
Sex	
Men Women	25 (65.8), 13 (34.2)
Access [n = 20]	
Internal jugular vein central venous	10 (50.0)
Arteriovenous fistula	7 (35.0)
Permacath	3 (15.0)
Comorbidities	
HTN	38 (100.0)
T2DM	25 (65.8)
Hepatitis C virus	1 (2.6)
Renal replacement therapy	21 (55.3)
Pregnancy	2 (5.3)
Post treatment	1 (2.6)
Severity	
Mild	3 (7.9)
Moderate	9 (23.7)
Severe	26 (68.4)
Laboratory values on admission, median (range)	
Total leucocyte counts (10^9/L)	11.7 (2.8-38.0)
Neutrophil count (10^9/L), mean (SD)	83.2 (9.1)
Lymphocyte count (10^9/L), mean (SD)	8.5 (0.9-32.0)
ESR (mm/h) [n = 34]	63.0 (1.0-114.0)
C-reactive protein (mg/dL) [n = 35]	87.0 (19.0-292.0)
Ferritin (mg/mL)	1.4 (0.1-5.6)
Interleukin-6 level (pg/mL) [n = 32]	22.3 (1.5-151.6)
Lactic dehydrogenase (U/L) [n = 37]	665.0 (400.0-1590.0)
Aspartate aminotransferase (IU/L)	37.5 (17.0-92.0)
Alanine aminotransferase (IU/L)	29.0 (5.0-77.0)
D-dimer (μg/mL) [n = 34]	2.2 (0.1-9.7)
CT severity score, mean (SD) [n = 34]	13.3 (5.8)
Oxygen support	12 (31.6)
High flow nasal cannula Mechanical ventilation Noninvasive ventilation	11 (28.9) 9 (23.7)
Low-flow oxygen	6 (15.8)
Clinical courses	
Heparin	38 (100.0)
Methylprednisolone	38 (100.0)
Remdesivir	38 (100.0)
Ivermectin	37 (97.4)
Azithromycin	34 (89.5)
Aspirin	22 (57.9)
Tocilizumab	3 (7.9)
Outcome	
Discharged	24 (63.2)
Death	14 (36.8)
Length of hospital stay [days], mean (SD) [n = 35]	14.9 (7.1)

Data shown as n (%), unless otherwise specified. *N = 38 unless otherwise specified. ESR, erythrocyte sedimentation rate; T2DM, type-2 diabetes mellitus.

Table 2. Comparison of clinical parameters across disease severity

Parameters	Moderate disease (n = 12)*	Severe disease (n = 26)**	P value
Age [years], mean (SD)	**63.9 (12.8)**	**54.5 (14.0)**	**0.055**
Sex			0.416
Men	9 (75.0)	16 (61.5)	
Women	3 (25.0)	10 (38.5)	
Access			-
Internal jugular vein central	[n = 5]	[n = 15]	
venous	3 (60.0)	7 (46.7)	
Arteriovenous fistula	1 (20.0)	6 (40.0)	
Permacath	1 (20.0)	2 (13.3)	
Comorbidities			
HTN	12 (100.0)	26 (100.0)	0.416
T2DM	9 (75.0)	16 (61.5)	-
Hepatitis C virus	-	1 (3.8)	
Renal replacement therapy	6 (50.0)	15 (57.7)	0.658
Pregnancy	-	2 (7.7)	-
Post treatment	-	1 (3.8)	-
Laboratory values on admission, median (range)			
Total leucocyte counts (10^9/L)	9.0 (5.0-21.0)	12.3 (2.8-38.0)	0.285
Neutrophil count (10^9/L), mean (SD)	80.1 (7.3)	84.7 (9.6)	0.153
Lymphocyte count (10^9/L), mean (SD)	12.5 (4.0-30.0)	7.8 (0.9-32.0)	0.036
ESR (mm/h)	[n = 10] 78.0 (52.0-101.0)	[n = 24] 61.0 (1.0-114.0)	0.405
C-reactive protein (mg/dL)	[n = 11] 87.0 (29.0-174.0)	[n =24] 87.5 (19.0-292.0)	0.776
Ferritin (mg/mL)	8.6 (0.1-2.0)	1.5 (0.1-5.6)	0.312
Interleukin-6 level (pg/mL)	[n =11] 47.3 (3.1-87.0)	[n =21] 21.0 (1.5-151.6)	0.284
Lactic dehydrogenase (U/L)	[n = 11] 593.0 (400.0-919.0)	692.0 (419.0-1590.0)	0.065

Aspartate aminotransferase (IU/L)	27.5 (20.0-92.0)	39.0 (17.0-83.0)	0.765
Alanine aminotransferase (IU/L)	21.0 (8.0-77.0)	30.0 (5.0-71.0)	0.314
D-dimer (μg/mL)	1.5 (0.1-9.7)	[n = 22] 2.7 (0.3-9.5)	0.678
CT severity score	[n = 11] 12.1 (5.4)	[n = 23] 13.8 (6.0)	0.423
Oxygen support			<0.001
High flow nasal cannula	6 (50.0)	6 (23.1)	
Mechanical ventilation	-	11 (42.3)	
Noninvasive ventilation	-	9 (34.6)	
Low-flow oxygen	6 (50.0)	-	
Clinical courses			
Heparin	12 (100.0)	26 (100.0)	-
Methylprednisolone	12 (100.0)	26 (100.0)	-
Remdesivir	12 (100.0)	26 (100.0)	-
Ivermectin	12 (100.0)	25 (96.2)	1.000
Azithromycin	11 (91.7)	23 (88.5)	1.000
Aspirin	6 (50.0)	16 (61.5)	0.725
Tocilizumab	-	3 (11.5)	-
Outcome			0.001
Improved	12 (100.0)	12 (46.2)	
Death	-	14 (53.8)	
Length of hospital stay [days], mean (SD)	[n = 11] 15.3 (5.2)	[n= 24] 14.7 (8.0)	0.820

Data shown as n (%), unless otherwise specified. *n = 12 and **n = 26 unless otherwise specified.
ESR, erythrocyte sedimentation rate; T2DM, type-2 diabetes mellitus.

Table 3. Clinical characteristics and disease-related symptoms in ESRD patients by survival status

Parameters	Discharged (n = 24)*	Death (n = 14)**	P value
Age [years], mean (SD)	57.8 (15.0)	56.8 (13.3)	0.830
Sex			0.391
Men	17 (70.8)	8 (57.1)	
Women	7 (29.2)	6 (42.9)	
Access			0.653
Internal jugular vein	[n = 12]	[n = 8]	
central venous	5 (41.7)	5 (62.5)	
Arteriovenous fistula	5 (41.7)	2 (25.0)	
Permacath	2 (16.7)	1 (12.5)	
Comorbidities			
HTN	24 (100.0)	14 (100.0)	-
T2DM	16 (66.7)	9 (64.3)	0.881
Hepatitis C virus	-	1 (7.1)	-
Renal replacement therapy	13 (54.2)	8 (57.1)	0.859
Pregnancy	-	2 (14.3)	0.057
Post treatment	1 (4.2)	-	-
Severity			0.006
Mild	3 (12.5)	-	
Moderate	9 (37.5)	-	
Severe	12 (50.0)	14 (100.0)	
Laboratory values on admission, median (range)			
Total leucocyte counts (10^9/L)	11.0 (5.0-21.0)	13.1 (2.8-38.)	0.315
Neutrophil count (10^9/L), mean (SD)	82.5 (8.2)	84.5 (10.7)	0.513
Lymphocyte count (10^9 cells/L), mean (SD)	9.3 (0.9-30.0)	7.0 (2.0-32.0)	0.113
ESR (mm/h)	[n = 21] 63.0 (1.0-114.0)	[n = 13] 79.0 (7.0-104.0)	0.576
C-reactive protein (mg/dL)	[n = 22] 81.5 (19.0-292.0)	[n = 13] 88.0 (50.0-216.0)	0.555
Ferritin (mg/mL)	0.9 (0.1-5.6)	1.7 (0.2-2.0)	0.100
Interleukin-6 level (pg/mL)	[n = 20] 22.3 (1.5-87.0)	[n = 12] 18.9 (7.0-151.6)	0.863
Lactic dehydrogenase (U/L)	[n = 23] 593.0 (400.0-1430.0)	850.0 (566.0-1590.0)	0.017
Aspartate aminotransferase (IU/L)	33.0 (17.0-92.0)	41.5 (21.0-69.0)	0.345
Alanine aminotransferase (IU/L)	26.0 (5.0-77.0)	30.0 (13.0-60.0)	0.161
D-dimer (μg/mL)	[n = 22] 1.9 (0.1-9.7)	[n = 12] 2.6 (0.3-7.6)	0.817
CT severity score	[n = 23] 13.8 (5.5)	[n = 11] 12.1 (6.5)	0.423
Oxygen support			<0.001
High flow nasal cannula	10 (41.7)	2 (14.3)	
Mechanical ventilation	-	11 (78.6)	
Noninvasive ventilation	8 (33.3)	1 (7.1)	
Low-flow oxygen	6 (25.0)	-	
Clinical courses			
Heparin	24 (100.0)	14 (100.0)	-
Methylprednisolone	24 (100.0)	14 (100.0)	-
Remdesivir	24 (100.0)	14 (100.0)	-
Ivermectin	24 (100.0)	13 (92.9)	0.185
Azithromycin	22 (91.7)	12 (85.7)	0.564
Aspirin	15 (62.5)	7 (50.0)	0.452
Tocilizumab	-	3 (21.4)	-
Length of hospital stay [days], mean (SD)	[n = 21] 18.1 (6.5)	10.0 (5.2)	<0.001

Data shown as n (%), unless otherwise specified. *n = 24 and **n = 14 unless otherwise specified.
ESR, erythrocyte sedimentation rate; T2DM, type-2 diabetes mellitus.

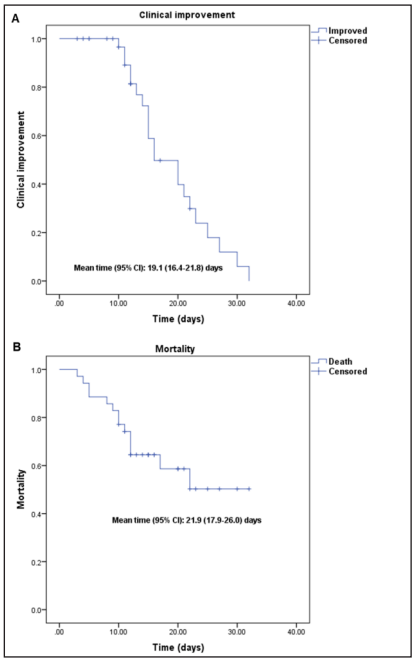

Figure 1. Kaplan-Meier plot for clinical improvement and mortality

DISCUSSION:

The present study prospectively analysed the clinical experience of remdesivir treatment among a cohort of ESRD patients with COVID-19 infection from Western India. The salient observations of this study are: a) the alarming rise in the prevalence of COVID-19 in ESRD patients aged 57.4 years; b) male preponderance; c) HTN and T2DM were the predominant coexisting conditions; d) incidence of elevated neutrophil count, ESR, CRP, ferritin, IL-6, LDH, and D-dimer were more common in patients with severe COVID-19 infection; e) Lymphocyte count was significantly lower in those patients with severe disease; f) around 63% of survival rate post remdesivir treatment; g) hospital stay was comparable in patients with severe and moderate disease; h) higher lactic dehydrogenase levels were found in those who died; i) the post-remdesivir laboratory parameters were within acceptable limits; j) no patient in the present cohort reported any immediate adverse effects after infusion of remdesivir; k) no abnormalities of renal function attributable to the drug were noted in any of the patients.

Male predominance in severe cases of COVID-19 and patients with ESRD was observed in this study is in concordance with the previous studies [14,15]. Similarly, a previous multicentric nationwide study turkey showed that men are more likely to be infected from COVID-19 than women [16]. A large-scale study that included patients with chronic liver disease and COVID-19 (N=3905) reported the prevalence of COVID-19 in patients with CKD and it was found to be highest in older individuals (>65 years) [17]. Another evidence-based multicentric study also showed COVID-19 was predominant among older patients aged >67 years with CKD [18]. Evidence from studies that included the adult Indian population demonstrated corroborating observations thereby suggesting COVID-19 is more prevalent among young Indian male patients [19,20]. Male sex and advanced age are associated with COVID-19 severity and mortality observed in this study are in concordance with the previous studies.

Underlying comorbid conditions can have a profound effect on COVID-19 outcomes in terms of rapid prognosis of disease and high risk of mortality and poor survival outcome [21]. A previous multicentric study from Turkey (N=1210) that included COVID-19 patients with kidney disease reported that HTN (62.8%), and T2DM (33.4%), ischemic heart diseases (30.1%), as most prevalent comorbidities followed by congestive heart failure (15.8%), and chronic obstructive pulmonary disease (13.6%) [16]. Seidel et al. reported high incidence T2DM, HTN, and coronary artery disease in COVID-19 infected patients [22]. Similarly, another study from India demonstrated a higher prevalence of T2DM and HTN in end stage kidney disease patients admitted with COVID-19 [20]. They are in line with the present study wherein HTN and T2DM were the most prevalent comorbidities observed among the present study population. Further, CKD patients with coexisting comorbid conditions such as HTN, T2DM and lung disease are associated with a poor prognosis of COVID-19 [23].

Previous study has reported alterations in the lymphocyte-to-neutrophil ratio (LNR) and neutrophil-to-monocyte ratio (NMR) in COVID-19 patients were in association with disease severity [24]. In the present study, the higher incidence of lymphopenia (lower lymphocyte count) was associated with disease severity. Similarly, Alberici et al. reported lower levels of lymphocytes in patients with severe COVID-19 disease [25]. Recent meta-analyses have shown that lymphopenia was associated with severity in COVID-19 infection [26]. Previous study corroborate with these findings suggesting a high incidence of lymphopenia in patients with COVID-19 disease who are critically ill and it also contributes to poor outcome [27]. Functional studies indicate that lymphocyte count plays a central role in the pathogenesis of severe COVID-19 [28]. Therefore, all this evidence along with the present study allude that the predominance of abnormal lymphocyte levels in severe disease than mild and moderate COVID-19 disease. An observational cohort study from India was reported on 48 patients requiring HD and those received remdesivir. The authors reported that 38 (79.2%) patients were discharged from the hospital, and remdesivir was not associated with any serious adverse effects in patients with severe COVID-19 pneumonia [11]. The present study reported a relatively lower survival rate of 63.2%. Among these, the majority of survival was observed in the moderate group (n = 12, 100.0%) compared to the severe group (n=12, 46.2%). These observations are in concordance with Selvaraj et al, study which reported overall survival rate of 64.3% among moderate and severe COVID-19 disease [29]. A short report of a retrospective cohort study from India indicated the association of remdesivir use with a survival benefit (hazard ratio [HR], 2.25; 95% CI, 1.27-3.97; P = 0.005) in patients with in severe COVID-19 pneumonia [30]. This relatively lower rate of mortality may be due to the initiation of remdesivir treatment at an appropriate time during the disease course. It has been suggested that remdesivir can be used with close monitoring in patients with renal disease.

A randomized control study from India indicated the association of remdesivir use with a survival benefit [Hazard ratio (HR): 1.29; 95% (confidence interval (CI), 1.12 to 1.49)] with shorter recovery time in patients who had received remdesivir than the control group (10 vs. 15 days). The mortality rates were lower in patients treated with remdesivir compared to the control group (6.7% vs. 11.9%) [31]. Garibaldi et al, reported a significant association between time to clinical improvement and remdesivir use [32]. The present study reported a relatively higher mortality rate of 36.8% than Aishwarya et al (20.8%) [11]. This relatively higher rate of mortality in the present study may be due to the co-existing risk factors and severity of COVID-19 in the deceased patients. The present results are similar to findings from previous study. A short report was conducted on 57 patients undergoing dialysis those who have received remdesivir. The results showed 52.2% were discharged from hospital post remdesivir treatment and remdesivir caused no significant renal function abnormalities [10]. In the present study, 63.2% of patients were discharged from the hospital, implying similar survival rates.

The present study showed a comparable duration of hospital stay in patients with moderate and severe disease. These observations contrast to previous studies in the literature [33,34]. A study by Aishwarya et al. reported prolonged hospital stay in patients with severe COVID-19 patients compared to moderate COVID-19 [11].

Elevated LDH values were found to be associated with an increased odd of developing severe disease and mortality in patients with COVID-19. The higher incidence of elevated levels of lactic dehydrogenase levels among patients who died is in accordance with the previous studies. Guan et al. reported a high incidence of elevated LDH levels (58.1% vs. 37.2%) in patients with severe disease compared to those with non-severe disease [35].

Similarly, another study from Spain demonstrated elevated levels of LDH levels (HR: 1.006 [1.001-1.011]; P=0.016) were strongly associated with increased hospital death [36]. The data revealed that the LDH findings at baseline could be a predictor of mortality.

The present study demonstrated the efficacy of remdesivir treatment in reducing laboratory data to normal levels post-treatment. Previous studies have shown a significant reduction in CRP and ferritin levels post remdesivir treatment

[11,37]. Other proinflammatory markers such as serum levels of D-dimer, LDH, and ferritin concentrations showed comparative reduction which was insignificant [29]. Thakre et al, showed a better improvement in elevated ALT and AST in patients treated with remdesivir treatment [10]. In a single centre study, patients treated with remdesivir demonstrated better improvement in laboratory parameters compared with the patients treated with standard treatment [32].

The current safety profile of remdesivir is still incomplete. Several evidences had shown that COVID-19 itself is involved in injuries of multiple organs including brain, heart, kidney, lung, liver, and gastrointestinal tract therefore it is complex to distinguish the underlying causes of adverse events during remdesivir treatment [38,39]. Moreover, the latest safety data from the previous retrospective study reported multiple-organ-dysfunction syndrome, septic shock, AKI, and hypotension as the most prevalent adverse events [7]. Additionally, an observational prospective study by Dhanapalan et al reported a single case of acute coronary syndrome on treatment with remdesivir [11]. No adverse events were reported among patients receiving remdesivir in both published double-blind and placebo-controlled studies evaluating remdesivir [31, 40]. These observations concord with the present study wherein, no patient reported any immediate adverse effects after infusion of remdesivir. Due to limited clinical experience with remdesivir for COVID-19, adverse drug effects need to be paid much attention to. The major limitations of this study is the small sample size.

CONCLUSION:

The use of clinical and biological parameters as early prognostic markers will be helpful to guide future management strategies. Clinicians should increase their awareness regarding COVID-19 in dialysis patients. Remdesivir therapy may be considered as a therapeutic option in the treatment of patients on dialysis with COVID-19. Future randomized clinical trials and real-world studies evaluating efficacy and safety of remdesivir in these patients with COVID-19 are required for validation of the available data.

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