Original Research Article

Retrospective analysis of clinical presentation and outcome of COVID-19 in hemodialysis patients in a tertiary care hospital from South India

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ABSTRACT

Background: COVID-19 (SARS-CoV-2) imposed a serious health challenge to patients on maintenance hemodialysis in developing countries like India. We are presenting our clinical experience, dialysis unit management and outcome of COVID-19 during this pandemic period (April 2020-May-2021).

Materials and Methods: This retrospective study was conducted on 60 patients admitted in our hospital due to COVID-19 infection. Patients were treated based on our institutional management protocol. For all patients, Blood sugar, complete haemogram, Blood urea, Serum Creatinine, Serum Electrolytes, Liver function test, serum C-reactive protein (CRP), Serum ferritin, D-Dimer level were done and CT- chest was done to assess the severity of lung involvement.

Results: Sixty patients on maintenance hemodialysis were admitted (n=60) in our hospital with COVID -19 and 32 (52.4%) were in mild, 14 patients each in moderate and severe categories. A spectrum of clinical presentations among the categories were asymptomatic in 23 (38.3%) patients, 20 (33.3%) had fever with cough and 17 (28.4%) had breathlessness. Males were 41 (68.3%), mean age was 53.81±12.77yrs. Median dialysis vintage was 27.7 (13.8-41.5) months and mortality rate 10%. Remdesivir was administered in 17 patients (28.3%). Neutrophil lymphocyte ratio (NLR), D-Dimer levels were significantly elevated with disease severity (<0.05) and Serum CRP and D-Dimer levels were significantly elevated among the mortality cases (<0.05).

Conclusion: Mortality was low in this study group (10%), NLR; D-Dimer levels were significantly elevated with disease severity. Serum CRP and D-Dimer levels were significantly elevated in the mortality group.

1. Introduction

In late 2019, a group of patients in Wuhan, China, developed severe respiratory distress. Further investigations revealed that it was due to corona virus-2, later named as SARS-CoV-2 commonly called Coronavirus disease (COVID-19). In March 2020, WHO declared a Global pandemic due to COVID-19. It is transmitted from person to person via droplets and close contact with an infected person up to 20% of infected patients develop moderate-to-severe COVID-19 disease. This COVID-19 imposed a serious health challenge to patients with chronic kidney disease, especially those on maintenance hemodialysis in developing countries like India.[1,2] Patients on maintenance haemodialysis are at high risk of acquiring infection by exposure to the infected person since they go for regular treatment at the hemodialysis center and the immunocompromised state of person makes them highly vulnerable for severe COVID disease.[3] With available published data, the exact incidence and mortality rates of COVID-19 among patients on dialysis

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are not established clearly. In this observational study, we present our clinical experience, dialysis unit management and outcome of COVID-19 in maintenance hemodialysis patients during the pandemic 2020-2021.

2. Materials and Methods

This observational study was conducted in the Department of Nephrology at Government Thiruvannamalai medical college and Hospital, Tamilnadu. Institutional ethics committee (IEC) approval was obtained before starting this study (Project No: 07/2021).

2.1. Study population

All patients with end-stage renal disease (ESRD) on maintenance hemodialysis who got admitted and tested positive for SARS-CoV-2 infection from nasopharyngeal swab analysis by RT-PCR were included in this study between April 2020-May-2021. Clinical data were obtained by reviewing case sheets from the hospital medical records department to categorize the patients. Patients were categorized into Mild, Moderate, and Severe (COVID-19) disease according to our Institutional Management Protocol. Clinical data including blood investigations and everyday progression of clinical status were taken for analysis. Specifically for those with moderate and severe disease the patient's clinical status was monitored periodically for oxygen (O2) requirement and administered remdesivir. All patients were given adequate dialysis in isolation as per the Ministry of Health and Family Welfare guidelines, Govt of India.[4]

2.2. Institutional management protocol (IMP)

For patients who got admitted to the COVID isolation ward in our hospital with ESRD on maintenance dialysis, an initial clinical assessment was performed, vitals were checked and routine blood investigations were taken, including Blood sugar, complete haemogram, Bl.urea, Serum Creatinine, Serum Electrolytes, Liver function test, serum C reactive protein (CRP), Serum Ferritin and D-Dimer level. After initial clinical stabilization, patients were subjected to computed tomography (CT) scan chest and the severity of pulmonary involvement was graded as grade-1 less than 25%, grade 2- 25% to 50%, grade 3- 50% to 75%, and grade-4 more than 75%. Same investigations were repeated when clinically indicated.

2.3. Case definitions

Mild, Moderate and Severe disease was defined as any one of the following signs or lab investigation present according to institutional management protocol.

2.4. Treatment regimen

According to Institutional Management Protocol, patient who had a moderate or severe disease was started with low molecular weight heparin 40 mg subcutaneously and intravenous Methylprednisolone 40 mg for 5 days, then 5mg/week dose tapered and stopped. On the day of dialysis, low molecular weight heparin was skipped and unfractionated heparin was used with a dose of 2500-unit bolus followed by 750units/hour. For all patients having grade 2 or above lung involvement, a third-generation cephalosporin was added to prevent bacterial superinfection. The hemodialysis schedule for every patient was decided based on clinical assessment every day and laboratory parameters.

2.5. Protocol for Remdesivir

The dose of Remdesivir was 2.5 mg/kg calculated according to dry weight of the patient and the maximum dose of Remdesivir was 100 mg, it was given 4 hours before the hemodialysis. Subsequently, 4 doses were given before each hemodialysis session. A liver function test was done every day to monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Further doses were withheld if the elevation was 5 times the upper limit of the normal level. Once the ALT and AST decreased to normal limits, further doses were administered, depending on the patient's clinical status.

2.6. Criteria for discharge

The decision to discharge was taken once the resolution of clinical symptoms for mild cases. For patients with moderate and severe disease, was based on the resolution of symptoms and ability to maintain oxygen saturation for the next consecutive days in case of those who had fluctuating oxygen saturation.[5]

2.7. Statistical analysis

Statistical analysis was performed for Qualitative variables, which are expressed as absolute numbers and percentages. Quantitative variables are expressed as mean ±standard deviation or as the median and interquartile range (IQR). Appropriate tests for statistical significance were used for comparisons between various groups by Fisher exact test for qualitative data, the independent samples t-test for continuous variables, and the Mann–Whitney U test for nonparametric data. Comparisons of parameters were done using the paired-sample t-test for continuous variables. For categorical variables, Fisher exact tests were conducted and a P-value<0.05 was considered statistically significant.

Table 1: Disease category parameters.

Parameters	Mild disease	Moderate disease	Severe disease
Oxygen saturation in room air (%)	>94%	94%-90%	<90%
Respiratory rate/min	<24/min	24-30/min	>30/min
Neutrophil lymphocyte ratio	3.1-5	5.1-7	>7
Serum CRP level(mg/L)	10-50mg/L	51-100mg/L	>100mg/L
Serum ferritin level(ng/ml)	400-600ng/mL	601-1500ng/mL	>1500ng/ml, Females>1000ng/ml
D-Dimer level (ng/ml)	<500ng/ml	500-1000ng/ml	>1000ng/ml
CT- Chest (lung involvement)	<25%	25%-75%	>75%

Table 2: Baseline characteristics

Parameters (n=60)	Values
Total no of patients	60
Male	41(68.3%)
Mean age (yrs)	53.81±12.77
Age >50 yrs	36(60%)
Co-morbid conditions:	
Diabetes mellitus	18(30%)
Hypertension	28(46.7%)
Diabetic and hypertensive	14(23.3%)
Dialysis vintage (median-IQR) months	27.7(13.8-41.5)
Underlying chronic kidney disease (CKD)	
Diabetic nephropathy	18(30%)
Chronic interstitial nephritis (CIN-CKD)	5(8.3%)
Chronic glomerular nephritis	21(35%)
Others	16(26.7%)
Symptoms at admission (n=60)	
Asymptomatic	23(38.3%)
Fever/cough	20(33.3%)
Breathlessness	17(28.4%)
Disease category (n=60)	
Mild	32(53.4%)
Moderate	14(23.3%)
Severe	14(23.3%)
Inpatient duration (Mean) Days	9.13±3.0
No of patients received remdesivir (n=60)	17(28.3%)
Lab values, median (IQR)	
Neutrophil-lymphocyte ratio (NLR)	9.5(4.7-14.2)
Aspartate aminotransferase (AST), IU/L	13.25(6.2-19.9)
Alanine aminotransferase (ALT),IU/L	15.75(7.9-23.6)
C-Reactive protein (CRP), mg/l	25.43(12.7-38.1)
S.ferritin, ng/ml	249.5(124.7-374.2)
D- dimer, ng/ml	341.5(170.7-512.2)
CT Chest grades, (n=60)	
Grade-1(<25%)	26(43.3%)
Grade-2(25-50%)	23(38.4%)
Grade-3(50-75%)	9(15%)
Grade-4(>75%)	2(3.3%)
Outcome, (n=60)	
Discharged	54(90%)
Death	6(10%)

Table 3: Parameters between disease categories

Parameters (n=60)	Mild	Moderate	Severe
Age, (Mean) Yrs	55.15±12.65	55.71±12.55	48.95 ±12.90
Age>50yrs	20 (33.3%)	10 (16.6)	6 (10%)
Males	22	9	10
Diabetes	11	4	3
Hypertension	11	7	10
Diabetic and hypertensive	10	3	1
Mean hospital days	8.8±2.3	8±1.8	10.8±4.6
No of patients with remdesivir	-	3	14
Dialysis vintage, months (IQR)	27.7 (13.8-41.5)	7.5 (3.7-11.2)	18 (9-27)
Underlying CKD			
Glomerular	12	8	1
CIN-CKD	3	2	-
Diabetic nephropathy	12	4	3
Others	9	4	3
Lab values,median (IQR)			
Neutrophil-lymphocyte ratio (NLR)	2.75(1.3-3.9)	6.2(3.1-9.3)	18.25(9.1-27.3)
Aspartate aminotransferase-ast, IU/L	19.5(9.75-29.2	13.2(6.6-19.8	10.8(5.4-16.2)
Alanine aminotransferase (ALT), IU/L	15(7.5-22.5)	18.5(9.2-27.7)	15.2(7.6-22.8)
Alkaline phosphatase (ALP), IU/L	26.5(13.2-39.7)	20.2(10.1-30.3)	53.5(26.7-80.2)
C-reactive protein (CRP),mg/l	53.5(26.7-80.1)	55.5(27.7-83.2)	22.3(11.1-33.4)
S.FERRTIN,ng/ml	285.9(142.9428.8	147(73.5-220.5	330(165-495
D-DIMER,ng/ml	332.5(166.2-498.7	212.7(106.3-319)	1443.6(721.82165.4)
CT chest grades			
Grade-1(<25%)	24	1	2
Grade-2(25-50%)	8	11	4
Grade-3(50-75%)	0	3	6
Grade-4(>75%)	0	0	2
Outcome (n=60)			
Discharged	32	12	10
Death	0	2	4

Table 4: Comparision of disease activity

Parameters (n=28)	Moderate (n=14)	Severe (n=14)	P-value
Age, (Mean) Yrs	55.71±12.55	48.95 ±12.90	0.166
Age>50yrs	10(16.6)	6(10%)	0.73
Males	9(32.1%)	10(37.7%)	1.000
Mean hospital days	8±1.8	10.8±4.6	**0.04**
No of patients with remdesivir	3	14	**<0.05**
Dialysis vintage,months (IQR)	7.5(3.7-11.2)	18(9-27)	1
Lab values, median (IQR)			
Neutrophil-lymphocyte ratio (NLR)	6.2(3.1-9.3)	18.25(9.1-27.3)	**0.01**
Aspartate aminotransferase -AST, IU/L	13.2(6.6-19.8)	10.8(5.4-16.2)	0.98
Alanine aminotransferase (ALT), IU/L	18.5(9.2-27.7)	15.2(7.6-22.8)	0.7
Alkaline phosphatase (ALP),IU/L	20.2(10.1-30.3)	53.5(26.7-80.2)	0.65
C-reactive protein (CRP),mg/l	55.5(27.7-83.2)	22.3(11.1-33.4)	0.80
S.ferritin, ng/ml	147(73.5-220.5)	330(165-495)	0.32
D-dimer, ng/ml	212.7(106.3-319)	1443.6(721.8-2165.4)	**<0.05**
Outcome(n=60)			
Discharged	10	12	0.64
Death	2	4	0.64

Table 5: Lab parameters after remdesivir

Parameters(n=17) median(IQR)	Before	After	P-value
Neutrophil-lymphocyte ratio (NLR)	13.5 (6.7-20.2)	6(1.5-4.5)	**<0.05**
C-Reactive protein (CRP), mg/l	26.2(13.1-39.3)	18.5(9.2-27.7)	0.45
S.ferritin, ng/ml	267.5(133.7-401.2)	239.5(119.7-359.2)	0.17
D-dimer, ng/ml	664.5(332.2-996.7)	152.5(76.2-228.7)	0.16
Aspartate aminotransferase- ast, IU/L	13.1(6.5-19.6)	9(4.5-13.5)	0.38
Alanine aminotransferase (ALT), IU/L	15.8(7.9-23.7)	14(7-21)	**0.04**
Alkaline phosphatase (ALP), IU/L	46(23-69)	40.5(20.2-60.7)	0.74

Table 6: Comparision between death and discharged

Parameters (n=60)	Discharged (n=54)	Death (n=6)	P-Value
Mean age (Yrs)	53.20±12.75	59.33±12.70	0.26
Age>50Yrs (n=36)	32(88.9%)	4(11.1%)	**0.07**
Males (n=41)	36(66.7%)	5(83.3%)	**0.41**
Remdesivir received (n=17)	11	6	**<0.05**
Hospital stay, (Mean) Days	9.4±2.8	6.5±3.8	**0.02**
Lab values, median (IQR)			
Neutrophil-lymphocyte ratio (NLR)	5.25(2.6-7.87)	19(9.5-28.5)	0.50
C-reactive protein (CRP), mg/l	22.66(11.3-33.9)	112.2(56.1-168.3)	**0.04**
S.ferritin, ng/ml	235.5(117.7-353.2),	390.5(195.25-585.7	0.30
D-DIMER,ng/ml	311.7(155.85-467.5)	5070.7(2535.3-7606)	**0.001**
Aspartate aminotransferase (AST), IU/L	12.25(6.12-18.37)	18.05(9.02-27.07)	0.73
Alanine aminotransferase (ALT), IU/L	15.25(7.6-22.87	35.2(17.6-52.8)	0.19

3. Results

The total number of patients with ESRD on maintenance dialysis who got admitted to the hospital was 60. All of them were included in this study, males predominating 41 patients (n=60, 68.3%). The mean age of the study population was 53.81±12.7 years and more than 50 years constitutes 60% of the patients (Table 2). People with diabetes of the 18(30%), 28 (46.7%) were hypertensive patients, and 14(23.3%) were both diabetic as well as hypertensive. Median dialysis vintage 27.7 (IQR=13.8-41.5) months (Table 2). The pattern of clinical presentation at admission was asymptomatic in 23 (38.3%) patients, fever and cough in 20(33.3%) and breathlessness in 17(28.4%) (Table 2). By the case definition, mild diseases were in 32(53.4%) patients, moderate and severe diseases were 14(23.3%) patients in each category (Table 2).

Among the study population, Remdesivir was administered for 3 patients with moderate disease and 14 patients with severe disease. With regard to investigations median Neutrophil-lymphocyte ratio (NLR) was 9.5 (IQR 4.7-14.2), median Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), serum CRP were 13.25 IU/L (IQR 6.2-19.9), 15.75 IU/L (IQR 7.9-23.6), 25.43 mg/l (IQR 12.7-38.1) respectively (Table 1). Median serum ferritin and D-Dimer levels were 249.5 ng/ml (IQR 124.7-374.2), and 341.5ng/ml (IQR 170.7-512.2) respectively (Table 2). CT-chest was taken for all patients in the study group and graded less than less than 25% in 26 patients; others 23, 9, and 2 patients had 25-50%, 50-75%, and >75%

lung involvement respectively (Table 1). The death rate among the study population was 10 % (Table 2).

Among the disease categories, prolonged inpatient days were seen in severe disease with a mean hospital stay of 10.8±4.6days and mild and moderate were 8.8±2.3 and 8±1.8 days respectively (Table 3). Median dialysis vintage was 27.7 (13.8-41.5) months in mild disease, moderate and severe diseases were 7.5 (3.7-11.2) and 18 (9-27) months respectively (Table 3).

Among the groups remdesivir was administered for 3 patients in moderate and 14 patients in severe disease. A statistically significant difference is seen in NLR (p=0.01) and D-Dimer levels (p<0.05) in moderate and severe disease groups (Table 4). At the time of admission, 17 (60.7%) patients in both moderate and severe disease categories required oxygen support, of which 8 patients were on high flow nasal oxygen (HFNO) therapy, 8 patients on O_2 mask, 1 patient required continuous positive airway pressure (CPAP) ventilation.

Remdesivir was administered to 17 patients, and lab investigations were repeated, which showed a statistically significant reduction in NLR and ALT levels[6] (Table 5). There was no significant difference seen in CRP, Serum Ferritin, D-Dimer, AST and ALP levels after Remdesivir administration (Table 5). Age more than 50 yrs had a significant correlation with disease severity (Table 6). Other parameters significantly correlated with disease activity were CRP, D-Dimer levels between two groups (Table 6).[7,8] There were no abnormality in the Liver function test

among remdesivir administered patients for both initial and repeated tests. There were no vascular access-related complications encountered in our study population. One patient had hemoptysis, and two patients had hypotension, and both complications were managed successfully.

4. Discussion

This observational study aims to describe data regarding clinical features, investigations, response to treatment and outcome of COVID -19 in maintenance hemodialysis patients. Clinical data regard to this population in COVID-19 is scarce. Goicoechea et al[1] published a study analyzing 36 patients with COVID-19 on hemodialysis patients from Spain. Significant findings are mortality rate was 30% and nonsurvivors had significant longer dialysis vintage, increased lactate dehydrogenase and C-reactive protein levels. Another similar data was published by Valeri et al which reported 30% mortality in 56 hemodialysis patients.[2] Our study population had a mortality rate of 10% among 60 patients, nonsurvivors had a significant correlation between CRP and D-dimer levels. Another difference was our study group had relatively younger patients with a mean age of 53 vs 71 yrs reported by the above cohort by Goicoechea et al.[1] Regarding comorbid diseases, hypertension in 35(97%) patients and diabetes in 26 (64%) patients were almost similar to our cohort. Clinical presentations were different, including fever in (67% vs 33%) patients, breathlessness (25% vs 28%), asymptomatic in our cohort was 38%. Main parameters from Goicoechea et al. associated with mortality among longer dialysis vintage and laboratory findings, namely high LDH and CRP levels. In our cohort, patients who presented with spo2 less than 90% at admission required immediate starting of nasal O2 or HFNO therapy and initiation of steroids and Remdesivir. A subset of patients from the above group developed fluctuating levels of O2 saturation and progressive clinical deterioration despite adequate treatment, leading to mortality.[9]

The impact of Remdesivir on COVID-19 mortality was not established clearly among maintenance dialysis patients. A recently published study by Dhanapalan aiswarya et al[9] shows early initiation of Remdesivir will shorten the time of recovery and discharge among the Indian population on maintenance dialysis, and it can be used safely under LFT monitoring.[10]

In our dialysis unit, all patients and healthcare workers were provided with triple-layer surgical masks as a measure to limit viral transmission. Recent observations show wearing a mask is an effective way to prevent viral transmission.[11] Separate dedicated hemodialysis machines were installed for COVID-19 positive patients in our hospital as per guidelines issued by the Ministry of Health and Family Welfare, Govt. of India.[4,6–8] Adequate isolation of COVID-positive or suspected patients from others and strict use of personal protective equipment (PPE) kits by all health care providers during dialysis will prevent spread of the virus.

5. Conclusion

This observational study showed patients on maintenance dialysis are at high risk of acquiring COVID-19 infection. Wearing a mask, personal hygiene and social distancing are important ways to avoid getting the infection. Every dialysis center must follow COVID-19 preventive protocol to limit viral transmission as per recommendations. At admission, patients on maintenance dialysis should be categorized and especially those with moderate and severe diseases need early initiation medication. Remdesivir should be started with other medications as early as possible with LFT monitoring.[5,10] Mortality was low in our study group (10%), NLR; D-Dimer levels were significantly elevated with disease severity. S. CRP and D-Dimer levels were significantly elevated in the mortality group. All patients who tested positive should be isolated and adequate Haemo dialysis should be given. Every day follow-up, glycemic control, hypertension control, and adequate diet and protein intake also contribute to early recovery.

6. Conflict of Interest

There are no conflicts of interest in this article.

7. Source of Funding

8. Acknowledgment

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