International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Respiratory Manifestations and Outcome of COVID-19 Positive Patients with CKD

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Abstract: ***Introduction: The prevalence of CKD (stage 1 to 5) among Indian population is 17.2%[1]. Among CKD patients; who appear most at risk for COVID-19 are those with a kidney transplant, due to immunosuppression, and those who undergo in-center hemodialysis treatments thrice weekly, due to inability to self-isolate. Patients with kidney disease also have other comorbidities, including hypertension, diabetes mellitus, and cardiovascular disease, that are risk factors for poor outcomes in COVID-19[2]. Aim: The study aimed to evaluate the presentation and outcome of COVID-19 in patients with CKD on MHD. Methods: Retrospective descriptive study included consecutive 50 patients who are known cases of CKD on MHD with confirmed diagnosis of COVID-19 who presented to Victoria Hospital from September 1. Data including demographic information, symptoms, laboratory examination (Hemoglobin, Total WBC count, NL ratio, C-reactive protein, serum Lactate dehydrogenase, D-dimer and serum Ferritin), initial chest Xray involvement, oxygen requirement during admission and clinical outcome (recovery and discharge/death) were obtained. These parameters were compared among both outcome groups. Results: The mean age ± SD of patients was 52.08±13.38 years. 74% were males. Of the total 50 patients; 37 (74%) recovered and 13 (26%) patients died. Most common co morbidity was hypertension (100%) followed by Type 2 diabetes mellitus (25%) and IHD (16%) respectively. 30% (n=15) patients were asymptomatic on admission and all recovered. The most common symptom on admission was cough (46%), followed by dyspnea (42%). The mean haemoglobin count is 9.10±1.66gm/dl and mean total WBC count is 8466±4490.78 cells/cu.mm. The mean NLR (26.01±25.94vs6.59±8.03), LDH (611.23±193.18U/L vs 382.14±151.84) and CRP (142.77±136.53mg/L vs 40.65±37.96mg/L) was higher in the population who died and was statistically significant. Conclusion: One third of the CKD patients on MHD were asymptomatic on presentation and it was associated with positive outcome. Patients who required NIV support initially on admission were at more risk of death. High NLR, elevated serum LDH levels, and raised serum CRP levels were associated with increased risk of mortality; hence these patients require more close monitoring.***

Keywords: CKD, COVID-19, Co-Morbidity diseases

1. Introduction

SARS-CoV-2, the virus that causes coronavirus disease 19 (COVID-19), has caused a major global pandemic[3]. Kidney disease is a common chronic disease. The prevalence of CKD (stage 1 to 5) among Indian population is 17.2%[1]. The patients with kidney disease who appear most at risk for COVID-19 are those with a kidney transplant, due to immunosuppression, and those who undergo in-center hemodialysis treatments thrice weekly, due to inability to self-isolate. Also patients undergoing maintenance hemodialysis (MHD) have abnormal immune systems because of the uremic state[4]. Patients with kidney disease also have other comorbidities, including hypertension, diabetes mellitus, and cardiovascular disease, that are risk factors for poor outcomes in COVID-19[2]. Reports indicate that patients receiving maintenance hemodialysis are at risk for severe illness with coronavirus disease 2019 (COVID-19)[5, 6], but information about this population of patients is limited. It would be interesting to know whether the clinical course of patients undergoing MHD having COVID-19 is different from that of other COVID-19 patients.

Aim of the study

- To evaluate the presentation and outcome of COVID-19 in chronic kidney disease (CKD) patients on hemodialysis.
- To compare the clinical parameters among the two outcome groups

2. Materials and Methods

- Study type : Retrospective observational study
- Place of study : Victoria hospital, Bangalore, Karnataka
- Study population: Consecutive 50 patients who are known cases of CKD on MHD with confirmed diagnosis of COVID-19 admitted from 1 September2020.
- Inclusion criteria: Confirmed diagnosis of COVID-19 through RT-PCR assay with samples obtained from nasopharyngeal/throat swab.Known case of CKD on MHD. Age older than 18 years old.
- Exclusion criteria: CKD patients who are not receiving dialysis, Age < 18 years.
- Data including demographic information, symptoms, laboratory examination (Hemoglobin, Total WBC count, NL ratio, C-reactive protein, serum Lactate dehydrogenase, D-dimer and serum Ferritin), initial chest Xray involvement, oxygen requirement during admission and clinical outcome (recovery and discharge/death) were obtained.
- Chest x-ray involvement documented as number of quadrants involved. An imaginary horizontal line was traced across the hilum to delineate upper and lower lung fields.
- Normal laboratory range for serum LDH is 240-480U/L.
- Normal laboratory range for serum CRP is <5mg/L
- Normal laboratory range for D dimer for adults is 0.05-0.5µgm/mL
- Normal laboratory range for serum ferritin is 30-400ng/mL

Statistical Analysis

Continuous variables are reported as mean (± SD) and categorical variables are expressed as frequency (percentage). Variables were compared across outcome groups (death vs. discharge).Student t-test was used for comparison of continuous data and Chi-square or Fischer's exact test was applied to compare categorical variables.P <0.05 was considered statistically significant.

3. Results

The mean age ± SD of patients was 52.08±13.38 years. 74% were males. Most common co morbidity was hypertension (100%) followed by Type 2 diabetes mellitus (25%) and IHD (16%) respectively. Of the total 50 patients; 37 (74%) recovered and 13 (26%) patients died.Mean duration of hospitalisation was 8.9±3.25 days. Age, co morbidities and duration of hospitalisation was comparable among both outcome groups.

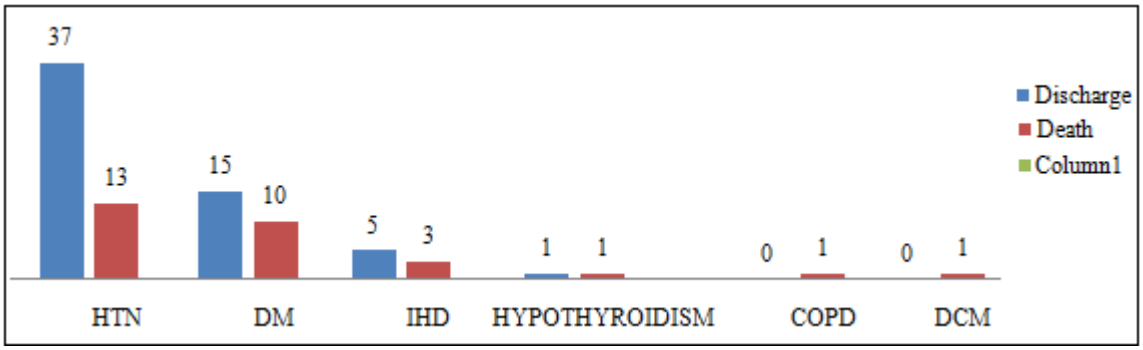

Figure 1: Distirbution of comorbidities among outcome groups

Table 1: Comparison of Patients' Baseline Characteristics Based on Final Disease Outcome

Variable		Total (n=50)	Discharged (n=37)	Death (n=13)	P value
Age		52.08±13.38	49.81±12.76	58.54±13.47	0.0517
Sex	Male	37 (74%)	31 (83.7%)	6 (46.2%)	0.02
	Female	13 (26%)	6 (16.3%)	7 (53.8%)	
Comorbidities					
HTN		50	37 (100%)	13 (100%)	1
TYPE 2 DM		25 (50%)	15 (40.54%)	10 (76.9%)	0.0507
IHD		8 (16%)	5 (13.51%)	3 (23.1%)	0.413
DCM		1 (2%)	0	1 (7.7%)	0.26
Hypothyroidism		2 (4%)	1 (2.7%)	1 (7.7%)	0.4563
COPD		1 (2%)	0	1 (7.7%)	0.26

30% (n=15) patients were asymptomatic on admission and all recovered. Overall, the most common symptom on admission was cough (46%), followed by dyspnea (42%), myalgia (32%), fever (20%), headache (12%) and altered sensorium (4%). All symptoms were equally distributed in both groups except dyspnea. Among patients who presented with dyspnea (n=21), 11 succumbed to death and 10 recovered which was statistically significant (p<0.05).

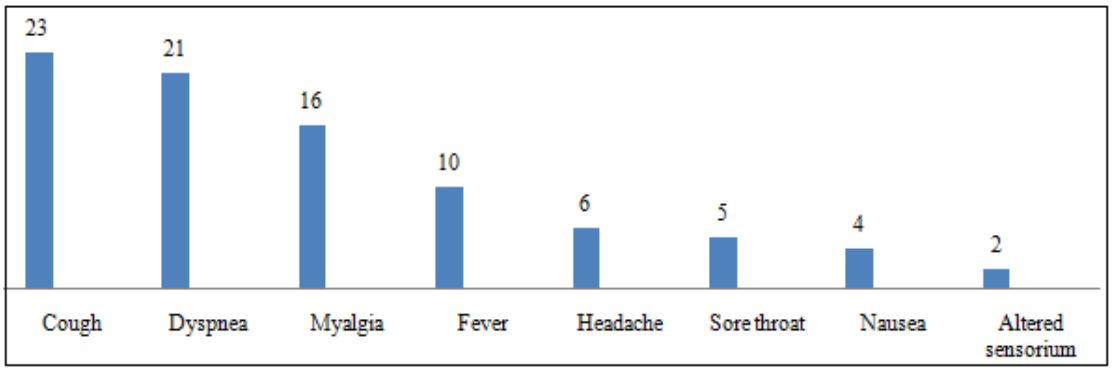

Figure 2: Distribution of symptoms in study group

Table 2: Comparison of Patients' Baseline Clinical Presentation Based on Final Disease Outcome

Variable	Total (n=50)	Discharged (n=37)	Death (n=13)	P value
Cough	23 (46%)	14 (37.8%)	9 (69.2%)	0.0618
Dyspnoea	21 (42%)	10 (27%)	11 (84.6%)	0.0006
Fever	10 (20%)	5 (13.5%)	5 (38.5%)	0.1009
Sore throat	5 (10%)	5 (13.5%)	0	0.3087
Myalgia	16 (32%)	13 (35.1%)	3 (23.1%)	0.5075
Nausea	4 (8%)	3 (8.1%)	1 (7.7%)	1
Headache	6 (12%)	4 (10.8%)	2 (15.4%)	0.6434
Altered sensorium	2 (4%)	0	2 (15.4%)	0.0637

In the initial chest X ray imaging, 12 (24%) patients had normal CXR, 40% had two quadrant involvement and 16% had all four quadrant involvement. Four patients had bilateral pleural effusion on CXR. All patients with normal CXR recovered whereas among 8 patients with all 4 quadrant involvement 5 succumbed to death which was statistically significant. (p=0.022)

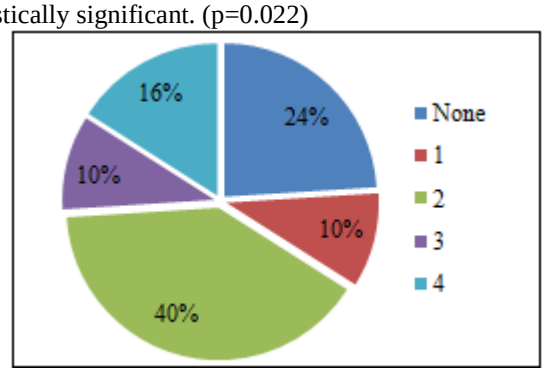

Figure 3: No. of quadrants involved in CXR

Table 3: No. of quadrants involved in CXR

Variable		Total (n=50)	Discharged (n=37)	Death (n=13)	P value
CXR quadrant involvement	1	5 (10%)	5 (13.5%)	0	0.3087
	2	20 (40%)	15 (40.5%)	5 (38.5%)	1
	3	5 (10%)	2 (5.4%)	3 (23.1%)	0.103
	4	8 (16%)	3 (8.1%)	5 (38.5%)	**0.0209**
	none	12 (24%)	12 (32.4%)	0	**0.0222**

46% (n=23) of the patients had room air saturation above 94% on admission and required no oxygen support, of which 21 recovered. However 2 patients worsened and died. 30% (n=15) patients received oxygen via face mask of which 13 recovered. Only 3 (6%) patients required oxygen via High flow nasal cannula and 2 patients recovered. Of the 7 (14%) patients who needed NIV support on admission 6 patients progressed to IMV and died, which was statistically significant with p value 0.0007. Only 2 patients directly received IMV on admission and both succumbed to death.

Table 4: Mode of oxygen delivery on admission

Variable	Total (n=50)	Discharged (n=37)	Death (n=13)	P value
MODE OF OXYGEN DELIVERY ON ADMISSION				
• No oxygen	23 (46%)	21 (56.7%)	2 (15.4%)	0.0119
• Face mask	15 (30%)	13 (35.1%)	2 (15.4%)	0.2938
• HFNC	3 (6%)	2 (5.4%)	1 (7.7%)	1
• NIV	7 (14%)	1 (2.7%)	6 (46.2%)	0.0007
• IMV	2 (4%)	0	2 (15.4%)	0.0637

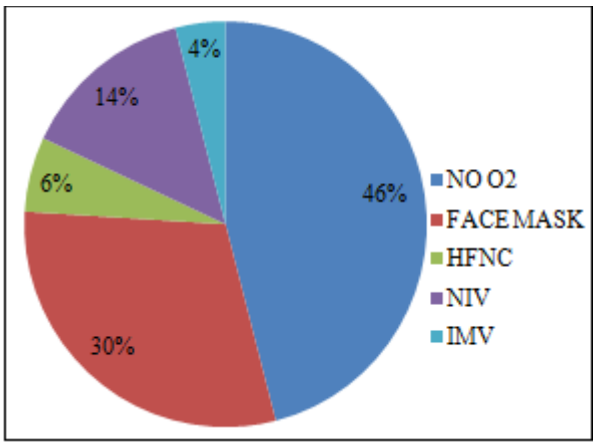

Figure 4: Oxygen Requirement During Admission

The mean haemoglobin count is 9.10±1.66gm/dl which is comparable among both outcome groups. The mean total WBC count is 8466±4490.78 cells/cu.mm. The mean WBC count is higher in death group compared to recovery group which is statistically significant (p<0.0001). The mean NLR of study population is 11.64±16.92. The NLR is higher in patients who died as compared to those got discharged (26.01±25.94 vs 6.59±8.03) which is statistically significant (p=0.0002). Mean serum LDH value of group is 441.7±190.75U/L. LDH values were higher among the death group compared to those who recovered (611.23±193.18U/L vs 382.14±151.84) and was statistically significant (p<0.0001).

The mean D-dimer of the study group is 1.61±2.35µgm/mL. The mean value of D dimer did not statistically differ among both outcome groups. The mean CRP of patients were 67.19±87.58 mg/L. The mean CRP levels among patients who died (142.77±136.53mg/L) was significantly higher compared to those who recovered(40.65±37.96mg/L) with p<0.0001. The mean serum ferritin value of the study population is 1218.55±689.66ng/mL which did not vary significantly among clinically recovered and dead patients.

Table 5: Comparison of laboratory findings based on final disease outcome

Variable	Total (n=50)	Discharged (n=37)	DEATH (n=13)	T value	P value
Haemoglobin	9.10±1.66	8.95±1.67	9.51±1.71	1.0338	0.3064
Total WBC count	8466±4490.78	7000±3099.10	12638.46±5296.15	4.6384	<0.0001
NLR	11.64±16.92	6.59±8.03	26.01±25.94	4.09	0.0002
Serum LDH	441.7±190.75	382.14±151.84	611.23±193.18	4.3549	<0.0001
D-dimer	1.61±2.35	1.26±0.95	2.63±4.28	1.8534	0.07
Serum CRP	67.19±87.58	40.65±37.96	142.77±136.53	4.1803	<0.0001
Serum Ferritin	1218.55±689.66	1187.92±711.54	1305.73±642.02	0.5259	0.6014

4. Discussion

According to the meta-analysis done by B M Henry et al, it was concluded that chronic kidney disease is associated with severe COVID-19 infection[7]. This study was conducted to evaluate the presentation and outcome of COVID-19 in chronic kidney disease (CKD) patients on hemodialysis and to compare the clinical parameters among the two outcome groups.

We have seen in our study and others, older age and comorbid conditions have higher incidence COVID-19 and also have greater risk of having severe manifestations as CKD patients have high comorbidity burden and are immunocompromised than general population[2, 8]. Like in most of the studies, men with CKD were more infected than women[2, 8] but in one study it was more common in women[9]

We found the most common comorbid condition to be HTN followed by diabetes mellitus, cardiovascular disease which was also the pattern in some studies[2]while cardiovascular disease was the most common condition in others[8].

The most common presentation was cough (46% n = 23), followed by dyspnea (42% n=23), but there was a good portion of patients who were asymptomatic (30% n=15) at admission. This was not the case with Valeri et al where fever followed by cough was the most common one[2] which was the same in the study done by Guan W et al[9], but in the one done by A Abrishami et al, dyspnea followed by cough was the commonest presentation[8].

On admission, 23 of the patients were maintaining in room air out of which 2 worsened and died, 2 were intubated on admission both of them died. 7 patients required NIV support of which 6 worsened were mechanically ventilated and died. Therefore, in general, the outcome of patients who required NIV and mechanical ventilation were poor with high mortality which is similar to other studies[2, 5].

We have found that patients presenting with mulifocal opacities have poor outcome. In our study, 40% patients had 2 quadrant involvement and 16% had involvement in all quadrants and all those with quadrant involvement succumbed to death. In most other studies, most of them had bilateral/ multifocal opacities and they also had high mortality[2, 8].

Patients with high total counts have higher tendency of requiring NIV and mechanical ventilation and are also at high risk of mortality similar to study by Valeri et al[2]. Eleven patients in our study had high total counts of which five were on NIV and two intubated. All except one atleast two quadrant involvement.Neutrophil-to-lymphocyte ratio (NLR) is a parameter to assess the inflammatory status of a subject[10] and in recent times it has proven to be of great significance especially in predicting the outcome of COVID 19 in patients[11].The mean NLR of study population is 11.64±16.92. the NLR is higher in patients who died as compared to those got discharged (26.01±25.94vs6.59±8.03), showing that the prognostic value of NLR holds true in our study also.

LDH is an intracellular enzyme found in cells in almost all organ systems, which catalyzes the interconversion of pyruvate and lactate[12]. It is released from the tissues following cytokine mediated severe inflammation and infection[13]. Therefore greater amounts of LDH will be released in severe COVID-19 infection. LDH is also elevated in thrombotic microangiopathy and as this is also seen in COVID-19, it also adds to the elevation of LDH in COVID-19 patients[14–16]. In our study, the mean serum LDH value was found to be is 441.7±190.75U/L with higher values among the death group (611.23±193.18U/L). Therefore we can conclude that patients with high LDH values have a poor outcome, as is the case in other similar studies[2, 8, 17].

D-dimer is one of the fibrin degradation products that is formed when plasmin cleaves fibrin and therefore elevated d-dimer indicates thrombolysis occuring in the body[18, 19]. It is observed that Covid-19 is associated with hemostatic abnormalities and elevated D-dimer levels[20]. Studies have also suggested that D-dimer may be used as an early marker of severity in COVID- 19 patients[18]. It was also observed that patients with increased D-dimer also had higher in-hospital mortality and can be used as biomarker for clinical outcome in patients with COVID-19[18, 20]. In our study, the mean D-dimer of the study group is 1.61±2.35µgm/mL which was high but didn't correlate statistically with the outcome of the patients.

C-reactive protein (CRP), an acute-phase protein, is a well-established marker of systemic inflammation and severe infection [21, 22]. Many studies have reported an association between elevated CRP levels and disease severity and outcome in COVID-19[21, 23]. The mean CRP of patients in our study was 67.19±87.58 mg/L. As seen in most of the studies[2, 8], in our study also CRP levels among patients who died (142.77±136.53mg/L) was significantly higher compared to those who recovered (40.65±37.96mg/L).

Ferritin is an acute phase protein which is elevated in any kind of inflammation in the body[24]and a mediator of immune dysregulation which contributes to cytokine storm[25, 26].As cytokine storm syndrome has been implicated as one of the major contributor in the severity and outcome of patients with COVID 19[27], it can be postulated that hyperferritinemia can act as marker of severity and outcome in COVID 19[5, 6, 25, 27]. This has been demonstrated in many studies as per Lino K et al[24]and the metanalysis done by B M Henry et al[7]. But in our study the mean serum ferritin value was found to be 1218.55±689.66ng/mL which did not vary significantly among clinically recovered and dead patients.

5. Conclusion

The results of the study show about one third of the CKD patients on MHD were asymptomatic on presentation and it was associated with positive outcome. Among symptomatics most patients manifested with cough and dyspnea similar to other non CKD patients.74% of the total patients recovered. Patients who required NIV support initially on admission were at more risk of death.

As compared to previous studies high NLR, elevated serum LDH levels, and raised serum CRP levels were associated with increased risk of mortality; hence these patients require more close monitoring. Due to the considerable number of asymptomatic cases it is necessary to implement and strictly follow all infection control measure including screening of body temperature and symptoms before entering dialysis or transplant clinics, universal masking, physical distancing and frequent hand hygiene within clinics, and, if possible, universal rapid testing for SARS-CoV-2 infection upon entry to dialysis clinics.

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