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# PREDICTORS OF UNFAVOURABLE OUTCOME IN PATIENTS ON MAINTENANCE HEMODIALYSIS WITH SARS COV 2 INFECTION

Nephrology

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## ABSTRACT

**Introduction:** The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was discovered in December 2019 in Wuhan, China, and quickly gave rise to a devastating pandemic. Due to uraemia-related immune system dysfunction, pro-inflammatory state , higher comorbidity burden, and the potential of cross-contamination from dialysis centres; patients on maintenance haemodialysis appear to be particularly prone to SARS-CoV-2 infection. **Materials and Methods** The retrospective observational study aimed to determine the clinical, biochemical, pharmacological, and radiological prognosticators of favourable outcomes in patients on maintenance haemodialysis with COVID-19 infection. It included all adult patients who were on haemodialysis therapy and were admitted to B.M.H.Gimcare hospital, Kanuur , Kerala ; with a positive real-time reverse transcription-polymerase chain reaction for SARS-CoV-2 between September 2020 to February 2021, identified from the electronic medical records system. **Result:** The mean age of the study's 21 males and nine females was 61.47 years; of these patients, nine succumbed to their illness. The mean age of the deceased (67.11 ± 12.34 years), dialysis vintage period (31.67 ± 7.48 months), and duration of hospital stay (13 ± 8 days) were higher than those of the survivors (59.05 ± 11.42 years, 15.71 ± 7.24 months, and 8.67 ± 4.23 days, respectively). The TLC at admission (14033.33 ± 14423.07 per µL), N/L ratio (6.27 ± 6.38), and lactate dehydrogenase serum (457.11 ± 245.26) were also significantly higher in those who had an unfavourable outcome. All cases on femoral dialysis access succumbed to this virus. **Conclusion:** We postulate that the outcome will be unfavourable in COVID-19 patients on heparin-free haemodialysis via femoral access, with higher total leukocyte levels, a raised neutrophil-lymphocyte ratio, lactate dehydrogenase and quick sequential organ failure assessment scores of more than two requiring invasive ventilatory support at admission.

## KEYWORDS

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), maintenance haemodialysis, COVID-19

## INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection emerged in Wuhan, China, in December 2019 and rapidly set off a pandemic. Since then, over forty million cases of SARS-CoV-2 have been reported globally. [1] In the general population, the 2019 coronavirus disease (COVID-19) has a mortality rate of around 6%, similar to mortality rate of SARS-CoV (10%) but lower than that of MERS-CoV (around 40%). [2]

Patients with comorbid conditions such as obesity, hypertension, diabetes mellitus (DM), cardiovascular disease, advanced age, or superimposed acute kidney injury (AKI) are more susceptible to SARS-CoV-2 infection and at a higher risk of intensive care admission or death.[3-7] However, these findings have been obtained mainly from studies on the general population. Patients on maintenance haemodialysis (HD) appear particularly vulnerable to SARS-CoV-2 infection due to uraemia-related immune system dysfunction, a pro-inflammatory state, increased comorbidity burden, frequent hospital admissions, and the risk of cross-contamination from the dialysis centres.[8,9]

Most studies with dialysis patients have focused on infection susceptibility and strategies to limit the disease spread. [10,11] To date, only isolated observations and small case series on prevalence and mortality rates have been reported in this population.[12-14]

Given these patients' increased vulnerability; their clinical presentation and outcomes could be different from those of the general population. Moreover, regional differences are also conceivable, as the outbreaks' extent and severity varied regionally. However, there is little data on Indian HD patients affected with COVID-19.

In this context, the present study was performed to evaluate the clinical, biochemical, pharmacological, and radiological predictors of favourable outcomes in patients on maintenance HD with COVID-19 infection.

## MATERIALS AND METHODS

This study was conducted in a quaternary level multispecialty hospital in South India - B.M.H.Gimcare hospital, Kanuur , Kerala ; catering to a population of nearly 1000 outpatients/day, 100 inpatients, and with an average COVID-19–ICU load of 75 to 100 patients/month during the peak season.

This retrospective, observational study included all adult patients who were on HD therapy and were admitted to our hospital with positive real-time reverse transcription-polymerase chain reaction (rRT-PCR) testing for SARS-CoV-2 between September 2020 to February 2021, identified from the electronic medical records (EMR) system.

Patients not on maintenance HD, those going on discharge against medical advice, or those requesting a transfer to another centre were labelled as outcome unknown and excluded from the analysis. All chronic kidney disease (CKD) patients who were not on HD and who had graft kidney failure and were reinitiated on HD were excluded.

Demographic and clinical data, radiological evaluation, and laboratory tests were retrieved from patients' EMR. Based on the clinical parameters at admission, the patients were allocated a quick sequential organ failure assessment (qSOFA) score, to determine the baseline severity of the disease at the time of presentation to the hospital. [15]

The data collected were coded and entered in a Microsoft Excel sheet, which was re-checked and analysed using the SPSS statistical software, version 22. Quantitative variables were summarised using mean and standard deviation (SD). The normality of distribution was checked using the Shapiro–Wilk test. Categorical variables were represented using frequency and percentage. Independent sample t-test and Mann-Whitney test were performed to determine the statistical significance of the difference between the means of the variables of the two independent groups based on the normality of distribution. Pearson's chi-square and Fisher's tests were used for comparing categorical variables between the groups. A p-value of $< 0.05$ was considered statistically significant.

## RESULTS

Thirty patients were included in the study: 21 males and 9 females. Their mean age was 61.47 years and the mean duration of in-hospital care 9.97 ± 5.84 days. Residual renal function, generating more than 150 ml of urine per day, was present in 40% (12) subjects, and the mean qSOFA score was 1.60 ± 0.81 at admission. Ventilator support at admission was required for 26.7% (8) of the cases. Nine patients succumbed to their illness.

**Table 1: Characteristics of the study group**

| PARAMETER | MEAN VALUE (%) |
|---|---|
| Age—years | 61.47 ± 12.09 |
| Sex—no. (%) | |
| Male | 21 (70) |
| Female | 9 (30) |
| Outcome—no. (%) | |
| Deceased | 9 (30) |
| Discharged | 21 (70) |
| No. of dialysis procedures during the in-hospital period | 4.80 ± 3.04 |
| Average inter-dialysis interval—days | 2.25 ± 0.97 |
| Comorbidities—no. (%) | |
| Hypertension | 26 (86.7) |
| Diabetes mellitus | 17 (56.7) |
| Coronary artery disease | 8 (26.7) |
| Hyperthyroidism | 2 (6.7) |
| Hypothyroidism | 2 (6.7) |
| Potassium—mEq/L | 4.90 ± 0.96 |
| Sodium—mEq/L | 135.20 ± 4.51 |
| Corrected calcium—mg/dl | 8.29 ± 1.12 |
| Phosphorus— mg/dl | 5.22 ± 1.93 |
| D-dimer—ng/ml | 2611.31 ± 2510.29 |
| CRP—mg/L | 76.55 ± 61.79 |
| Haemoglobin—g/Dl | 9.96 ± 2.18 |
| Total leucocyte count—WBCs/mic L | 8580.85 ± 8847.94 |
| Neutrophil to lymphocyte ratio at admission | 3.96 ± 4.15 |
| LDH—U/L | 309.23 ± 179.26 |
| AST—U/L | 45.03 ± 42.33 |
| ALT—U/L | 26.53 ± 20.37 |
| Bilirubin— mg/dl | 0.75 ± 0.26 |
| Albumin— mg/dl | 3.15 ± 0.67 |
| HbA1C % | 7.17 ± 1.78 |
| CT score CORADS | 4.43 ± 1.43 |

CRP—C-reactive protein, LDH—lactate dehydrogenase, AST—aspartate transaminase, ALT—alanine transaminase, HbA1C—glycated haemoglobin

Twenty (66.71%) of the patients were dialysed via an arteriovenous fistula (AVF), 8 via internal jugular catheter access, and two through the femoral central line. All patients were on thrice-weekly HD before the illness, and the mean dialysis vintage was 20.05 ± 10.33 months. Mean systolic BP at the time of admission was 143.06 ± 22.42 mm of Hg, oxygen saturation 93.33 ± 6.14%, pulse rate 90.80 ± 14.99/minute, haemoglobin 9.96 + 2.18 g/dL, ferritin 789.60 ± 371.38 µg/L, and vitamin D 24.50 ± 12.34 ng/mL.

The mean age of the deceased cases was 67.11 ± 12.34 years and that of the survivors 59.05 ± 11.42 years. Deceased patients had a longer dialysis vintage (31.67 ± 7.48 months) when compared to those who survived the disease (15.71 ± 7.24 months).

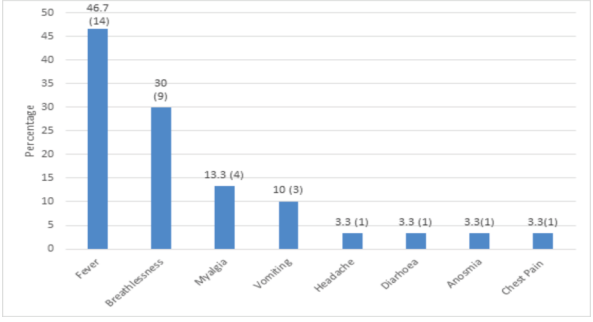


**Figure 1: Symptoms at presentation**

**Table 2: Association of various factors with the outcome**

| Variable | Outcome | | P-value |
|---|---|---|---|
| | Deceased (N = 9) | Discharged (N = 21) | |
| Age | 67.11 ± 12.34 | 59.05 ± 11.42 | 0.085 |
| Sex | | | |
| Male | 8 (38.1) | 13 (61.9) | 0.210 |
| Female | 1 (11.1) | 8 (88.9) | |
| HD access | | | |
| AVF | 1 (5) | 19 (95) | < 0.001 |
| IJC | 6 (75) | 2 (25) | |
| Femoral | 2 (100) | 0 | |
| No. of days of hospital stay | 13 ± 8 | 8.67 ± 4.23 | 0.037 |
| No. of dialysis procedures during the IP period | 5.78 ± 4.49 | 4.38 ± 2.17 | 0.257 |
| Average inter-dialysis interval in days | 2.69 ± 1.24 | 2.07 ± 0.79 | 0.148 |
| Diabetes Mellitus | 6 (35.3) | 11 (64.7) | 0.691 |
| Hypertension | 9 (34.6) | 17 (65.4) | 0.287 |
| D -dimer—ng/mL | 3609.64 ± 2858.69 | 2183.45 ± 2286.41 | 0.054 |
| C-reactive protein— mg/L | 98.87 ± 59.50 | 66.98 ± 61.65 | 0.182 |
| Haemoglobin—g /dL | 9.63 ± 2.43 | 10.10 ± 2.12 | 0.389 |
| Total leucocyte count at admission-WBC/micro L | 14033.33 ± 14423.07 | 6244.07 ± 3345.58 | 0.049 |
| Neutrophil to lymphocyte ratio at admission | 6.27 ± 6.38 | 2.97 ± 2.30 | 0.039 |
| Lactate dehydrogenase—U/L | 457.11 ± 245.26 | 245.86 ± 92.07 | 0.006 |
| Vitamin C supplementation | 2 (11.1) | 16 (88.9) | 0.013 |
| Vitamin D supplementation | 3 (16.7) | 15 (83.3) | 0.102 |
| Steroids | 9 (47.4) | 10 (52.6) | 0.011 |
| Furosemide | 4 (66.7) | 2 (33.3) | 0.049 |
| Torsemide | 5 (45.5) | 6 (54.5) | 0.225 |
| Heparin-free dialysis | 4 (66.7) | 2 (33.3) | 0.049 |
| Ventilator support | 7 (87.5) | 1 (12.5) | < 0.001 |
| qSOFA score | 2.56 ± 0.52 | 1.19 ± 0.51 | < 0.001 |

## DISCUSSION

To date, few reports have been published on the impact of COVID-19 on patients undergoing maintenance HD, especially in the Indian context.

Fever is the most common symptom noted in the general population, irrespective of the geographical region (99% in China and 94% in the United States). [16,17] In our cohort of HD patients, fever was found less frequently (43%), similar to data reported by Yiqiong et al. [18] This could be due to a lower inflammatory response in HD patients with COVID-19, secondary to the decreased number of lymphocytes and lower serum levels of inflammatory cytokines than in the general population.

In our patients, dyspnoea and cough were common (38% and 35%, respectively) but less frequent than in the general population (60.4% and 41.1%, respectively). [19] This is comparable with data from European (44% had a cough) and Asian HD patients (26% had dyspnoea and 37.4% suffered from cough). [12, 9] The lower rates of

gastrointestinal manifestations noticed in our study concurs with the observations in a Spanish cohort of COVID-19 patients on HD. [12] Although in studies from the general population, smell and taste alteration were reported in up to 64% of cases, this was not a major complaint in our study cohort. [19]

Zou et al. found that fever, dyspnoea, and elevated D-dimer were independent risk factors for death in HD patients with COVID-19, but our study failed to demonstrate a statistical significance for D-dimer and CRP as a predictor of mortality. However, we observed that the patients in the non-survivor group were more dyspnoeic with mean SpO2 levels of 90.11 ± 8.24 % when compared to the survivor group with a mean SpO2 of 94.71 ± 4.58 at the time of admission, attaining a statistical significance. [20]

Currently, the pharmacological approach to treating SARS-CoV-2 infection in kidney disease patients comprises two steps. In the first step, antiviral drugs and monoclonal antibody cocktails are tried due to their alleged inhibitory effect on viral entry and replication. In the second step, which typically begins after 7–10 days from the onset of symptoms, immunosuppressive and immunomodulatory drugs are used because of the hyperinflammatory and cytokine release syndromes. [21] So far, there are no randomised controlled trials on therapies for COVID-19 patients who are on maintenance HD. Goicoechea et al. in a retrospective, observational study on 36 HD patients reported a possible benefit of corticosteroids and azithromycin treatment, which was not found in our cohort. [12]

Wu et al. conducted a retrospective, observational study on COVID-19 patients in Wuhan comparing the clinical presentation and outcome of 49 patients on HD with 52 hospitalised patients without kidney failure. They found a significantly higher rate of complications, including shock, acute respiratory distress syndrome, arrhythmia, and acute cardiac injury, in patients on HD. Additionally, compared with controls, more patients on HD received non-invasive ventilation (25% versus 6%), and the mortality rate was higher (14% versus 4%). [22]. The mortality rate in our cohort of maintenance HD patients (30%) was higher than that reported by Yiqiong et al. from China (4.7%) but similar to observations from Spain (30.5%). [18, 12]

In our study, we noticed that mortality was higher among those on femoral dialysis access probably due to a higher incidence of secondary bacterial infection. The higher total leukocyte levels, an elevated neutrophil-lymphocyte ratio, and increased LDH, predicted an unfavourable outcome. Vitamin C supplementation may have a mortality benefit in this group, but this finding needs to be verified with larger randomised control studies. We suggest torsemide as the diuretic of choice in indicated cases due to the mortality benefit noticed in our study population. Heparin-free dialysis is indicated only if there is a high chance of bleeding or thrombocytopenia with heparin or if a coagulopathy is present. A higher qSOFA score and the requirement of invasive ventilatory support at admission time may predict an unfavourable outcome. Mortality may be lesser in HD patients with COVID-19 as compared to the general population possibly due to impaired cellular immune function and inability to mount cytokines storms. [18]

Our work has the typical limitations of a retrospective, observational study, as well as has a small sample and was conducted during a pandemic when healthcare resources had to be re-routed for patient care, and medical research other than that on COVID-19 has paused. The study findings may need to be confirmed with larger randomised trials, but our study still contribute to the ever expanding literature on this new, highly contagious , and potentially fatal infection.

## CONCLUSION

SARS-CoV-2 infection increases mortality and morbidity in patients on maintenance HD while increasing the cost of treatment. We find that outcomes will be unfavourable in COVID-19 patients on heparin-free HD via femoral access, higher total leukocyte levels, raised neutrophil-lymphocyte ratio, LDH, and q SOFA score of more than two requiring invasive ventilatory support at admission.

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**Competing Interest**: None that is known.

## Ethical considerations

This study was approved by the Research & Scientific Committee, Institutional Human Ethics Committee (EC/ GIMCARE/ NEPRO/ OBSV/03.21/002), and approval for publication was granted by Medical Director,B.M.H. Gimcare Hospital, Kannur.

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