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Monitoring System, Evolution and Prognosis in Renal Patients on Haemodialysis Infected by Severe Acute Respiratory Syndrome Coronavirus 2

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Abstract

Aim: The novel coronavirus disease 2019 (COVID-19) was first described in Wuhan, China, in December 2019. It has since spread worldwide, leading to high morbidity and mortality. Patients with chronic renal failure on dialysis who also have a confirmed diagnosis of active infection represent a risk group because infections are the second cause of death in this group, followed by immunosuppression caused by the weakening of the innate immunity by uremic toxins. This study aimed to describe the clinical characteristics of patients undergoing haemodialysis who also have a confirmed diagnosis for COVID-19 and its association with short-term outcomes.

Methods: This retrospective study recruited adult patients undergoing permanent renal replacement therapy with a confirmed diagnosis of COVID-19 through a polymerase chain reaction test on nasopharyngeal swabs. It was conducted from May to October 2020 at two private hospitals of Barranquilla, Colombia.

Results: 56 patients were registered with stage 5 chronic kidney disease and COVID-19 disease. The average patient age was 62 years, 66% were male, and 45% were on dialysis for hypertensive nephropathy. Although 37% presented with residual diuresis, this did not influence the results. Furthermore, 95% of cases were hypertensive, 30% diabetic, 20% heart disease, 12% chronic obstructive pulmonary disease and 12% obesity. The most frequent symptoms were dyspnea (86%) and fever (54%). 80% of the patients were assigned imaging scores of 4 and 5 based on the COVID-19 Imaging Reporting and Data System imaging classification. In addition, 9% of cases required invasive mechanical ventilation and 23.2% of the cases died.

Conclusion: We conclude that patients with permanent chronic kidney disease on dialysis are more vulnerable to developing complications and die due to COVID-19.

Keywords: COVID-19; Haemodialysis; SARS-CoV-2; Chronic kidney disease; Infectious disease

Introduction

The novel coronavirus disease 2019 (COVID-19) was first described in Wuhan, China, in December 2019. It has since spread worldwide, leading to high morbidity and mortality, in addition to economic and social collapse, and was declared a pandemic on 11 March, 2020 [1].

According to the Center for Disease Control and Prevention and the World Health Organization, the global mortality rate associated with COVID-19 ranges from 0.3% to 10% among different populations [2]. These values could be affected by differences in age, fragility and existing comorbidity, showing worse outcomes for patients with

comorbidity diagnosis such as arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cancer and chronic kidney disease [3].

In addition, patients with chronic renal failure on dialysis represent a risk group on their own because infections are the second cause of death in this group owing to their secondary immunosuppression that is caused by the weakening of their innate immunity by uremic toxins and associated malnutrition. Furthermore, these patients present a higher amount of proinflammatory cytokines in their peripheral blood, which is accompanied by an increased expression of Toll-like receptors in monocytes and granulocytes, resulting in increased inflammation and tissue dysfunction. In addition to this, there exist comorbidities and "logistic" exposures because these patients need to visit haemodialysis centers 3-4 times per week which increases the vulnerability of this patient group [4,5].

Therefore, these individuals are more susceptible to SARS-CoV-2 infections and to be associated with developing complications such as acute respiratory failure, arrhythmias and shock of different etiologies (i.e., distributive, cardiogenic, obstructive and hypovolemic shock). Shock is the first cause of death in 7% of cases of COVID-19 and a contributing factor in 33% of the patients. Among renal patients on haemodialysis, global mortality ranges from 23% to 30.5%, mainly in elderly patients and in those who have been dependent on treatment for a longer time. According to data from the available literature, one of every four patients on dialysis with COVID-19 will not survive [6,7].

This is why, for this group of patients and their healthcare providers, the greatest efforts must be directed at prevention, strengthening all structural biosecurity measures and all logistical stages related to their treatment, including transfers from and to medical centers [8]. However, some of these recommendations are impossible to follow in Latin America because of vast inequalities in terms of health access and lack of resources [9,10].

Although COVID-19 has been described as being more severe to this group of patients, the factors affecting its development and prognosis are not yet fully known and further evidence is still needed. In this research, we present the experience of a fourth-level medical center with patients undergoing chronic haemodialysis who also presented with COVID-19. We describe and correlate factors associated with poor prognosis and mortality in this population group.

General Objective

The aim of this study is to describe the clinical characteristics of patients undergoing permanent renal replacement therapy such as haemodialysis, with a confirmed diagnosis of COVID-19 and its association with short-term outcomes.

Material and Methods

Study design

This retrospective study included adult patients with stage 5 chronic kidney disease undergoing permanent renal replacement therapy such as haemodialysis with a confirmed diagnosis of COVID-19 through polymerase chain reaction (PCR) test on nasopharyngeal swabs. This study was conducted from May to October 2020 at two state-of-the-art private hospitals located in Barranquilla, Colombia.

We registered data about patients' baseline characteristics, clinical evaluation at the moment of diagnosis, laboratory parameters, radiological findings and short-term results. The information was collected by nephrologists who reviewed patients' medical records. The radiological images were evaluated by a specialist who classified the patterns that were found according to the classification by COVID-19 Imaging Reporting and Data System (CO-RADS) [11].

The basic characteristics of patients included demographic data (age and sex), cause of admission to dialysis and length of treatment, presence of residual diuresis and presence of co-morbidities (diabetes, hypertension, heart disease, obesity and COPD).

Regarding the clinical presentation of a patient at the moment of diagnosis, the presence or absence of the following symptoms was registered: fever, cough (productive or nonproductive), headache, diarrhea, vomiting, dyspnea, fatigue, myalgia, ageusia and anosmia. The application of any assisted ventilation method (invasive or noninvasive) was also registered.

Laboratory tests were performed on the first day of hospitalization and were repeated during a follow-up period, according to the directions from the treating doctor. The data extracted from the results included the count of white blood cells, neutrophils, lymphocytes, haemoglobin, platelets, prothrombin time, international normalized ratio (INR), partial thromboplastin time, glycemia, creatinine, blood urea nitrogen, urea, sodium, potassium, chlorine, calcium, magnesium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (direct and indirect), lactate dehydrogenase (LDH), D-dimer, C-reactive protein, ferritin and troponin I.

The X-ray patterns were analyzed from the images available from X-rays or tomographies of the thorax, following the directions of the doctor who treated them at the beginning of the hospitalization.

Patients were followed from the beginning of their hospitalization until their deaths or discharge from the hospital, with these two factors being the variables of the analyzed outcome. Hospital release was determined by the cure of the clinical illness.

Statistical analysis

Quantitative variables are summarized in mean and standard deviation (SD) or median and interquartile range (IQR). Qualitative variables are summarized through absolute, relative and percentage frequencies. Quantitative variables among groups defined by the outcome were compared through t-test comparison of two means in independent samples or Mood's median test. Qualitative variables were compared through the Chi-squared test for association or Fisher's exact test. Associated probability values lower than 0.05 were considered statistically significant.

Results

Over the period studied, 56 patients were registered in any of the two referred hospital centers with stage 5 chronic kidney disease. They were undergoing a permanent renal replacement therapy such as haemodialysis and had a PCR test positive for COVID-19.

Basic characteristics

Table 1 reports the basic characteristics of the analyzed group of patients. Patients' average age was 62 years (51-69.5). The youngest patient was 31 years old and the oldest was 83 years old. The composition of the group of patients by sex was 66% men and 34% women.

The most frequent cause of hospitalization for dialysis was hypertensive nephropathy in 45% of cases. This was followed in importance by a combination of diabetic renal disease with hypertensive nephropathy (21%) and exclusive diabetic renal disease (12%). The average duration of the dialysis treatments was 39.5 months (24-63). The most recent patient had been treated for 3 months and the oldest had been treated for 13 years.

Table 1: Basic characteristics of patients included in the study.

Characteristic	Summary	
Age (years), Mean(SD) /Median(IQR)	59.9 (12.6) / 62.0 (51.0-69.5)	
Sex, count (%)		
Male	37	(66.1)
Female	19	(33.9)
Cause of hospitalization in dialysis, count (%)		
Hypertensive nephropathy (HTA)	25	(44.6)
Diabetic renal disease (DBT)	7	(12.5)
HBP+DBT	12	(21.4)
Glomerulonephritis	4	(7.1)
Chronic uropathy	3	(5.4)
HBP+Chronic uropathy	2	(3.6)
Others	3	(5.4)
Length of dialysis (months), Mean (SD) / Median(IQR)	46.3 (33.15) / 39.5 (24.0-63.0)	
Residual Diuresis, count (%)	21	(37.5)
Co-morbidities, count (%)		
HBP	53	(94.7)
DBT	17	(30.4)
Heart disease	11	(19.7)
COPD	7	(12.5)
Obesity	4	(7.1)

HBP: High Blood Pressure, DBT: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease.

Approximately 37% of patients had residual diuresis. As for co-morbidities, hypertension was the most frequent, being observed in 95% of patients. Diabetes mellitus (30%), heart disease (20%), COPD (12%) and obesity (7%) were observed to a lesser extent.

Clinical manifestations and laboratory parameters at the beginning of hospitalization

The most frequent symptom at the beginning of hospitalization was dyspnea, observed in 86% of cases. The second most frequent symptom was elevated body temperature, registered in 54% of patients, followed by nonproductive cough in 41% of cases. Diarrhea, ageusia and anosmia were less frequent symptoms, presented in at least 10% of cases (Table 2).

Regarding radiological findings, over 80% of patients were assigned imaging scores of 4 and 5 according to CO-RADS classification. About 59% of the patients were category 5 and 23% were category 4. There were no patients belonging to category 2, and the remaining 18% were equally divided between categories 1 and 3.

Half of the hospitalizations were registered in the Emergency Care Unit of the hospital centers, whereas the other half was either admitted to the general room (30%) or to the intensive care unit (ICU) (20%).

Approximately 32% of patients required noninvasive assisted ventilation at the beginning of the hospitalization, and an additional 9% required invasive mechanical ventilation; thus, a total of 41% of patients required assisted ventilation) (Table 2).

Table 3 reports the median (IQR) of the analyzed laboratory parameters in patients at the beginning of their hospitalization.

Table 2: Symptoms and radiological characteristics at the beginning of hospitalisation.

Characteristics	Count (percentage)	
Symptoms		
Dyspnea	48	(85.7)
Fever	30	(53.6)
Nonproductive cough	23	(41.1)
Fatigue	18	(32.1)
Myalgia	13	(23.2)
Productive cough	10	(17.9)
Vomiting	7	(12.5)
Headache	6	(10.7)
Diarrhea	5	(8.9)
Ageusia	5	(8.9)
Anosmia	4	(7.1)
CO-RADS Pattern		
1	5	(8.9)
2	0	(0.0)
3	5	(8.9)
4	13	(23.2)
5	33	(59.0)
Admission Unit		
Emergency care	28	(50.0)
Hospitalization	17	(30.4)
ICU	11	(19.6)
Assisted ventilation		
Invasive	5	(8.9)
Noninvasive	18	(32.1)

Outcome

The patients' follow-up ended with a hospital discharge in 77% of patients and with an in-hospital death rate of 23.2% in the remaining patients (Table 4).

Table 5 shows the comparison of basic characteristics, symptoms and laboratories among discharged patients and deceased patients. Deceased patients represent an older age than the discharged patients. Among the deceased patients, a higher percentage of men than women were observed, although differences did not show significance.

Among co-morbidities, only the presence of COPD showed a significant association with the outcome, this one being more frequent among deceased patients. Regarding symptoms, a significant association was found between the outcome and the presence of headaches, which were also more frequent among deceased patients. Myalgia and fatigue were also more prevalent symptoms among deceased patients, although there was no significant difference.

The CO-RADS classification of radiological findings showed a higher frequency in category 4 and 5 patients among the deceased. However, differences among groups were not statistically significant.

The need to administer assisted ventilation, whether invasive or not, was more frequent among patients who passed away, although only one significant difference was detected in the case of noninvasive ventilation.

Among laboratory parameters, significant differences were found between both groups in the count of white blood cells, neutrophils and lymphocytes. White blood cell count was significantly lower

Table 3: Laboratory parameters at the beginning of hospitalization.

Laboratory parameters	N	Median (IQR)		Reference values
White blood cells	51	5100	(14.9-9300.0)	4.500-11.000 × mm^3
Hemoglobin (g/dl)	51	10.7	(9.2-11.6)	13-16 g/dl
Platelets	51	194000	(122500.0-261500.0)	150.000-450.000 × mm^3
Neutrophils	50	2861.5	(71.5-6634.5)	1.800-6.400 × mm^3
BUN mg/dl	50	51.4	(36.1-70.0)	9-20 mg/dl
Creatinine (mg/dl)	49	8.3	(6.5-11.1)	0.6-1.2 mg/dl
Sodium (mmol/l)	47	138	(135.3-141.5)	137-145 mEq/l
Potassium (mmol/l)	47	5	(4.5-5.7)	3.5-5.1 mEq/l
Lymphocytes	46	416	(26.62-897.5)	1.200-3.600 × mm^3
Chlorine	44	103.5	(99.7-108.4)	98-107 mEq/l
C-reactive Protein	39	32.4	(9.0-52.2)	0-1 mg/dl
LDH (U/L)	36	416.7	(303.0-533.2)	120-246 U/L
TP (seg)	27	12.6	(11.7-14.3)	9.1-12.1 seg
INR	19	1	(1.0-1.1)	-
TTP (seg)	27	32	(30.0-39.5)	25-45 seg
Troponin I (0-0.03 ng/ml)	27	0.1	(0.0-0.2)	0-0.03 ng/ml
Blood sugar (mg/dl)	26	116.5	(95.0-146.7)	70-105 mg/dl
Urea (mg/dl)	26	130.6	(93.3-178.5)	15-38 mg/dl
D-dimer	24	469	(149.6-1858.5)	0-255 ng/ml
Ferritin	22	462.9	(211.2-1285.2)	20-250 Ug/L
GOT	20	32	(24.7-61.2)	17-59 UI/L
GPT	19	27	(18.3-59.5)	11.4-44.53 UI/L
Total Bilirubin (mg/dl)	17	0.7	(0.5-0.9)	0.2-1.3 mg/dl
Direct Bilirubin (mg/dl)	16	0	(0.0-0.2)	0.0-0.3 mg/dl
Indirect Bilirubin (mg/dl)	16	0.2	(0.1-0.4)	0.0-1.1 mg/dl
Magnesium (mg/dl)	11	2.1	(1.7-2.2)	1.6-2.3 mg/dl
Calcium	7	8	(1.1-9.0)	8.4-10.2 mg/dl

n = number of patients for whom each parameter was analysed.
Prothrombin Time (PT), International Normalized Ratio (INR), Partial Thromboplastin Time (PTT), Aspartate aminotransferase (GOT), Alanine aminotransferase (GPT), Lactate dehydrogenase (LDH).

Table 4: Follow-up results.

Outcome	Count (%)
Deceased	13 (23.2)
Discharged	43 (76.8)

among deceased patients, and neutrophil and lymphocyte counts were significantly higher among deceased patients than in discharged patients. As for the parameters associated with coagulation time, the differences were only significant in the case of INR, although higher values were observed in the deceased patient group.

Discussion

Although the COVID-19 pandemic represents a risk for the overall population, this risk is higher for immunocompromised patients, including those on chronic haemodialysis. These patients are more susceptible because of their older age and multiple co-morbidities, as documented by this research. The average age was 59.9 years old and, among the main co-morbidities, we found arterial hypertension (94.7%), diabetes mellitus (30.4%), heart disease (19.7%), COPD (12.5%) and obesity (7.1%) [12]. Findings are consistent with reports from other studies where arterial hypertension is present in over 80% of patients undergoing haemodialysis treatment and 40% of patients with diabetes mellitus. These two conditions are the main causes for chronic kidney disease, both in our study sample and in the medical literature [13-15].

Furthermore, previous studies have shown that the presence of these same co-morbidities is usually associated with a worse prognosis for renal patients. As observed in our study, in the case of those patients also having COVID-19, COPD was the co-morbidity most significantly associated with death. This is in line with other publications, including those including COPD and COVID-19 patients that show a 60% mortality rate in comparison with the 55% mortality rate in patients without COPD [16].

In contrast, 50% of patients without previous renal disease who were admitted to the ICU were diagnosed with COPD as co-morbidity [17]. Moreover, residual renal function was present in 37.5% of cases, although no significant relation with mortality was found despite the fact that it reduces the constant inflammation that patients face on haemodialysis [18].

Among the most frequent clinical manifestations, we found dyspnea (85.7%), fever (53.6%), nonproductive cough (41.1%), fatigue

Table 5: Comparison of characteristics according to outcome.

Characteristics	Deceased (n=13)		Discharged (n=43)		p-value
Age, Median (IQR)	67.0	(56.5-71.0)	59.0	(50.0-69.0)	0.264
Sex (male), n (%)	11	(85.0)	26	(60.0)	0.181
Comorbidities, n (%)					
DBT	4	(30.8)	13	(30.2)	0.999
HBP	13	(100.0)	40	(93.0)	0.999
Heart disease	5	(38.5)	6	(14.0)	0.104
Obesity	1	(7.7)	3	(7.0)	0.999
COPD	4	(30.8)	3	(7.0)	0.043(*)
Symptoms at the moment of diagnosis, n (%)					
Fever	7	(53.8)	23	(53.5)	0.999
Nonproductive cough	6	(46.2)	17	(39.5)	0.753
Productive cough	2	(15.4)	8	(18.6)	0.999
Headache	4	(30.8)	2	(4.6)	0.021(*)
Diarrhea	1	(7.7)	4	(9.3)	0.999
Vomiting	3	(23.1)	4	(9.3)	0.334
Dyspnea	11	(84.6)	37	(86.0)	0.999
Fatigue	7	(53.8)	11	(25.6)	0.089
Myalgia	6	(46.2)	7	(16.3)	0.055
Ageusia	0	(0.0)	5	(11.6)	0.580
Anosmia	0	(0.0)	4	(9.3)	0.563
Co-RADS classification, n (%)					
1	0	(0.0)	5	(11.6)	0.379
3	0	(0.0)	5	(11.6)	
4	4	(30.8)	9	(20.9)	
5	9	(69.2)	24	(55.8)	
Assisted ventilation, n (%)					
Invasive mechanical	3	(23.1)	2	(4.6)	0.070
Noninvasive	8	(61.5)	10	(23.2)	0.017(*)
Laboratory, Median (IQR)					
White blood cells	3300.0	(8.1-7300.0)	9360.0	(4925.0-12297.5)	0.040(*)
Neutrophils	7298.0	(4112.0-11058.8)	90.3	(69.8-4949.3)	0.008(*)
Lymphocytes	667.0	(454.0-978.8)	214.5	(20.9-925.0)	0.007(*)
D-dimer	700.0	(246.0-2803.5)	362.5	(10.0-1827.3)	0.132
C-Reactive Protein	30.4	(14.0-53.5)	33.0	(6.3-55.5)	0.476
LDH	402.5	(272.5-839.4)	416.7	(302.9-541.7)	0.999
Ferritin	808.5	(131.4-1686.0)	462.9	(211.3-1220.6)	0.999
PT	14.5	(12.4-17.0)	12.0	(11.2-13.9)	0.173
INR	1.1	(1.1-542)	1.0	(1.0-1.0)	0.006(*)
TTP	34.0	(28.8-46.2)	31.6	(30.0-39.2)	0.173

(*) Significant at 5%.
HBP: Arterial hypertension, DBT: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, Prothrombin Time (PT), International Normalized Ratio (INR), Partial Thromboplastin Time (PTT), Aspartate aminotransferase) (GOT), Alanine aminotransferase (GPT), Lactate Dehydrogenase (LDH).

(32.1%), myalgia (23.2%) and, less frequently, vomiting (12.5%), headache (10.7%), diarrhea (8.9%), ageusia (8.9%) and anosmia (7.1%). This is in line with other studies about the frequency of the main manifestations. However, values are lower for gastrointestinal tract-associated symptoms and well below the reported values for the general population regarding taste and smell (34%-87%) [19-21]. It is striking that fever is the main symptom registered for the general population, reaching 99% of cases. However, it was less frequent among our patients, possibly because of the association with a lower immune response [22].

Regarding X-ray patterns, we used the CO-RADS classification. Approximately 59% of the X-rays were inside CO-RADS-5, turning CO-RADS-6 once reported PCR positive. This correlates to what is typically observed in radiological findings of alveolar-interstitial patterns and frosted glass images [11,23].

Regarding the standard laboratory tests of the patients, we found a significant association to leukopenia at the expense of lymphopenia, which could be explained because the constant state of uraemia leads to the deterioration of the immune function and response. Moreover,

lymphopenia is a marker for poor prognosis [16,24]. Additionally, there is a significant association between mortality and high INR, which could be explained by sepsis-induced coagulopathy in these patients [25]. Nonetheless, there was no association with the complementary tests that are typically described in the literature for COVID-19.

Furthermore, 19.6% of cases required hospitalization in the ICU, 8.9% mechanical ventilation and 23.2% of the total patients that died. These findings bring additional evidence to the findings of some Spanish and Italian medical centers that showed that dialysis type chronic kidney disease represents a very poor prognosis in those patients who develop SARS-CoV-2 infection, with a mortality rate of 28% which is well over the estimated 1%-2% for the general population [5,26].

Preliminary studies in China had claimed that patients undergoing haemodialysis did not represent a vulnerable group due to their incapacity to create an immune response that leads to cytokine storm. Some metanalysis studies support that patients with kidney failure in terminal stage dialysis are highly susceptible to COVID-19 due to their immunosuppression [27-29]. Some authors suggest that the death of these patients is not directly related to the infection but other causes [26].

Our findings show that, in the studied population of patients undergoing permanent haemodialysis, these have a higher risk of contracting and developing severe forms of COVID-19. We also found that a great percentage of cases lead to death, which could be due to the immune changes induced by chronic uraemia, which lowers the activity of neutrophils, monocytes, T cells and B cells [26,30].

The absence of effective treatments with proven evidence requires strengthening healthcare, biosecurity, individual and social measures that allow creating the most adequate protection, global health care measures and prevention against the COVID-19 pandemic; while the vaccine and their mid-term and long-term results are evaluated. It is essential to establish all necessary measures inside nephrology services and dialysis centers to protect patients and healthcare providers, avoiding risky transfers, crowded waiting rooms, maintaining distance among chairs, using personal protection equipment for personnel and patients (according to regulations) and medical isolation when there are SARS-CoV-2 infection symptoms or there has been a close contact. If the patient requires hospitalization, it is also necessary to speed up all interventions that could save the life of the patient, above all ensuring the correct oxygen saturation in blood, strictly following up the clinical and laboratory variables so that we can anticipate the appearance of severe multiorgan alterations. This will allow patients to receive the available therapeutic measures with proven evidence.

Conclusion

As a result of the data disclosed and the obtained correlations, it is possible to conclude that patients having permanent chronic kidney disease on dialysis are more vulnerable to develop complications and die due to COVID-19. This possibility increases in patients with additional chronic diseases such as hypertension and diabetes mellitus. Therefore, it is especially necessary to create strategies for the protection and individual care in patients with COPD because of the closer relationship observed in our research among this chronic condition (stage 5 renal disease in haemodialysis), COVID-19 and death.

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Conflict of Interest

The authors of this article declare that there is no conflict of interest.

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