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RESEARCH ARTICLE OPEN ACCESS

Prevalence and Outcomes of COVID-19 Infection among Hemodialysis Patients in Nephrology-accredited Training Institutions in the Philippines

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Abstract:

Introduction: Patients on maintenance hemodialysis are at an increased risk of SARS-CoV-2 infection and mortality. This study aimed to determine the prevalence of COVID-19 antibodies in a large sample of patients on dialysis in PSN-Accredited Nephrology Training Institutions.

Methods: This retrospective cohort study was conducted in partnership with eighteen medical centers with PSN-Accredited Nephrology Training. Adult patients who had RT-PCR confirmed COVID infection from March 2020 to March 2022 were included. Patient records were then collected, and pertinent data were collected using a standardized form. It was then transferred to an electronic database for further analysis.

Results: There were 785 hemodialysis patients who developed COVID-19 during the mentioned period, having an overall prevalence of 5.1%. Of these, 171 patients (22%) died during their hospitalization. There was a higher proportion of hypertensive patients and dyspnea on presentation in the mortality group. The mortality group also has significantly higher hematocrit and inflammatory markers (D-dimer, Ferritin, CRP). Based on multivariate analysis, the presence of cytokine storm, sepsis, higher D-dimer values, use of extracorporeal circuit, and tocilizumab were significant factors of mortality.

Discussion: This study has the largest number of centers involved in any COVID studies done locally. It showed variations in terms of complications and how the patients were managed.

Conclusion: This study found that the prevalence and mortality rate of COVID-19 infections are higher among patients receiving hemodialysis than in the general population. These findings highlight the importance of vaccination and other preventive measures to protect this vulnerable population.

Keywords: Dialysis, Infections, Chronic kidney disease, Epidemiology, COVID-19, Critical care.

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1. INTRODUCTION

COVID-19 had a significant impact on the hemodialysis (HD) population. It has led to outbreaks, as seen in two dialysis centers in Lombardy, Italy [1]. Other aspects of management among these patients were greatly affected. Due to infection control policies, most elective surgeries were advised to be postponed, leading to delays in the creation of arteriovenous fistula [2]. Due to concerns of immune suppression from medications, there was also a delay in performing kidney transplants. In the United Kingdom, about 1,670 kidney transplant opportunities were lost, which led to 6,317 active patients on the kidney-alone waiting list instead of 4,649 individuals [3].

Studies documenting the incidence of COVID-19 in dialysis patients are limited. In the case of the hemodialysis population, articles published in the past were case reports [4] or case series [5]. But with the steady rise of cases, more studies were presented. In one study done at the dialysis center of Renmin Hospital in Wuhan, China, where the first outbreak of the disease was seen [6], forty-two of 230 maintenance hemodialysis patients (18.26%) were diagnosed with COVID-19 infection during the study period. The duration of the study was done during the start of the outbreak (January 14, 2020) up to the control of the epidemic on March 12 that same year. Fifteen HD patients (6.52%), including 10 COVID-19-diagnosed died.

Another study documented COVID-19 cases in a dialysis center at a University Hospital in Madrid, Spain [7]. Among the 90 patients in their unit, 37 (41.1%) were diagnosed with COVID-19 infection, 36 of whom were confirmed by a positive PCR test. About 60% of patients were symptomatic, with 16 of the cases needing hospital admission and 6 resulting in death. From this data, they have modified their policies and organized a dialysis area for COVID-19 cases with protocols for infection control and management.

A study done in an in-patient dialysis center in a hospital in Paris, France, saw forty-four COVID-19 patients who were on dialysis. The majority were hemodialysis patients, and only five patients were on peritoneal dialysis (PD). Three of these patients were switched to hemodialysis during their course in the hospital [8].

In a multicenter study involving four large medical centers in Wuhan, China, among eight hundred eighteen patients on PD, eight were found to be positive for COVID-19. They have similar symptoms, radiographic changes, and lab findings to the other COVID-19 cases in general. Six recovered, and two of these patients died [9].

Regarding prevalence studies, there are two large studies. In a retrospective study by a national dialysis provider in the United States, 438 of 7948 (5.5%) maintenance dialysis patients developed COVID-19. Factors associated with developing COVID-19 infection were male sex, African American race, in-center dialysis (*vs* home dialysis), treatment at an urban clinic, residence in a congregate setting, and greater comorbidity. Of these maintenance dialysis patients with COVID-19, 109 (24.9%) died. Older age, heart disease, and markers of frailty were associated with mortality [10]. Meanwhile, in Germany, a study that involved 238 dialysis centers, the prevalence was 14% and the mortality for COVID-19 dialysis patients was 30% [11].

The European Renal Association - European Dialysis and Transplant Association has developed ERACODA (ERA-EDTA COVID-19 Database for patients on dialysis or living with a kidney transplant) that also collects individual data of dialysis and kidney transplant patients who were infected with COVID-19 [12]. Upon examination of its data collection form, certain details were not gathered, such as medications given, specific respiratory modality if required, and adjustment of dialysis dose. Our database aims to collect local, comprehensive data to understand the epidemiology, clinical course, and outcomes of COVID-19 infection among our hemodialysis and peritoneal dialysis patients. This will guide us in making recommendations as to the diagnosis and management of dialysis patients to improve survival for dialysis patients. It will lead to better outcomes and avoid unnecessary burdens to family members of dialysis patients, and minimize transmission of infection to other people. The study's main objective is to describe the prevalence, clinical profile, and clinical outcomes (*i.e.*, hospital stay, mortality) of hemodialysis patients infected with COVID-19.

2. METHODOLOGY

2.1. Research Design

The study is a retrospective cohort study, reviewing the charts of COVID-19 patients seen from March 2020 to March 2022. This was initiated and funded by the Philippine Society of Nephrology. The board officers were not directly involved in the creation of the protocol, study implementation, and analysis of results. The study was carried out in eighteen (18) tertiary hospitals with Philippine Society of Nephrology accreditation for subspecialty training.

The Principal Investigator was responsible for initial study design and protocol development. The draft was forwarded to all institutions above and was approved by the various Sections of Nephrology. Meetings were held with the primary investigators of the other institutions for the final protocol draft that was submitted to the Single Joint Research Ethics Board and other Ethics Committees. The Primary Investigator and the Co-Investigator made the necessary revisions, if needed, in coordination with the Principal Investigator.

2.2. Subjects

All patients who are on maintenance hemodialysis for at least 3 months duration, admitted from March 2020 to March 2022, were included in the study. The following will be excluded: 1) Suspected or Probable patients with COVID-19 infection, not confirmed by RT-PCR testing, 2) Patients who went home against medical advice, and 3) Patients who refused any form of management, such as use of certain medications, mechanical ventilation, use of hemoperfusion, or change in mode of renal replacement therapy. Purposive sampling of all eligible patients will be performed.

2.3. Sample Size Determination

Based on a previous study conducted in Germany [13], the computed prevalence of COVID-19 infection in dialysis patients is 14%. Using the formula $n = Z^2 \times P \times (1-P) / d^2$ (where Z = constant, p = Prevalence, and d = Precision) [14] with a confidence interval of 95% and a precision of 0.05, the computed sample size for this current study is 186 for hemodialysis patients who developed COVID-19.

2.4. Data Collection

All site investigators underwent orientation and training before the study in: 1) data extraction from medical records to a data collection form (DCF) [See Supplement Material] encrypted electronic mailing with an assigned password for data protection to the designated research assistants. Missing data or any data with potential error were verified by the research assistants with the respective site investigators to ensure the accuracy of the data.

All eligible chronic kidney disease (CKD) patients maintained on hemodialysis were recruited for the study. The primary investigator assigned a patient code. The patient code consists of the institution-specific alpha code that the main investigator designated, as well as a numeric code specific to each patient. Basic demographic and clinical information were obtained, including the outcomes.

The electronic data registry has security features (such as the use of passwords and multi-factor authentication) and can only be accessed with the permission of the Philippine Society of Nephrology to minimize harm or risk due to unauthorized data breaches. Any use of the data for future studies is also subject to approval by the Society.

2.5. Data Analysis

Prevalence was determined by the proportion of all admitted dialysis patients who developed COVID-19. Frequency distribution will be generated. The demographic characteristics: age above and below 60 years, male or female, and presence of co-morbidities and will be reported as percentages. Patients who developed cytokine storm will be reported as a percentage. Need for mechanical

ventilators, vasopressors, and medications prescribed will be reported as a percentage. Length of hospitalization and Intensive Care Unit (ICU) stay will be reported as the mean number of days ± standard deviation. Mortality was reported in percent.

Independent Sample T-test, Mann-Whitney U test, and Fisher's Exact/Chi-square test were used to determine the difference in mean, rank, and frequency, respectively, between died and survived patients. The odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant predictors for mortality. The stepwise method was utilized to determine the final multivariate model. All statistical tests were two-tailed tests. The Shapiro-Wilk test was used to test the normality of the continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at the 0.05α-level of significance. STATA 13.1 was used for data analysis.

3. RESULTS

An amount of 785 unique hemodialysis patients had COVID infection during the study period. Considering the hemodialysis population of regions covered by these institutions, the prevalence of COVID is 5.1% among hemodialysis patients. Among institutions, the Medical City reported the greatest number of cases (112), followed by Southern Philippines Medical Center, Chong Hua Hospital, St. Luke's Medical Center- Quezon City, and Veterans Memorial Medical Center (Table 1).

In the study population, 171 patients died while admitted, accounting for 22% of mortality. There is no significant difference between the survivors and non-survivors based on demographic data (Table 2). In terms of co-morbidities, more than three-quarters of the subjects were hypertensive, with a significantly higher proportion among non-survivors. Almost three-fifths of the subjects were diabetic, and almost a third with dyslipidemia, but there was no statistical difference between the two groups. In terms of maintenance medications, more deceased patients also used diuretics and insulin, while more survivors had a higher proportion of taking calcium carbonate and sevelamer. A higher percentage of survivors also had supplementary epoetin, with most of them using epoetin alfa. The average epoetin dose among users was not statistically significant.

Table 1. Breakdown of cases by institutions.

-	Cases	-	Cases
Angeles University (AUFMC)	9	Makati Medical Center (MMC)	37
Bicol Regional (BRTTH)	60	National Kidney (NKTI)	27
Cebu Doctors (CDUH)	22	Philippine Children's (PCMC)	12
Chinese General Hosp (CGH)	41	Perpetual Succour Hospital	23
Chong Hua Hospital (CHH)	81	St Luke's Medical Global	28
East Avenue Medical (EAMC)	29	St Luke's Medical QC	71
Fatima University (FUMC)	2	Southern Philippines (SPMC)	108
Jose Reyes Memorial (JRMMC)	8	The Medical City (TMC)	112
Manila Doctors Hospital (MDH)	44	Veterans Memorial (VMMC)	71

Table 2. Clinical & demographic profile of the adult HD patients who developed COVID.

-	Total (n=785)	Died (n=171, 22%)	Survived (n=614, 78%)	-
	Frequency (%); Mean ± SD; Median (IQR)			
Age	62.23 ± 15.84	61.78 ± 16.35	62.68 ± 16.14	0.754
Sex	-	-	-	0.307
Male	444 (56.60)	103 (60.23)	342 (55.70)	
Female	341 (43.40)	68 (39.77)	272 (44.31)	
Dialysis Duration, months	24 (12 to 43)	24 (12 to 48)	24 (12 to 41)	0.963
Cause of CKD	-	-	-	-
Diabetes mellitus	398 (50.70)	87 (50.88)	311 (50.65)	0.946
Hypertension	239 (30.45)	49 (29.87)	190 (30.94)	0.882
Glomerulonephritis	103 (13.12)	22 (12.87)	81 (13.35)	0.643
Obstructive Uropathy	17 (2.17)	5 (2.92)	13 (2.10)	0.845
Others	28 (3.56)	8 (4.67)	19 (3.09)	0.327
Comorbidity	-	-	-	-
Hypertension	597 (76.05)	142 (83.04)	455 (74.10)	**0.031**
Diabetes mellitus	468 (59.62)	99 (57.89)	369 (60.09)	0.562

(Table 2) contd.....

-	Total (n=785)	Died (n=171, 22%)	Survived (n=614, 78%)	-
	Frequency (%); Mean ± SD; Median (IQR)			
Dyslipidemia	237 (30.19)	51 (29.82)	186 (30.29)	0.696
Stroke	209 (26.62)	56 (32.75)	153 (24.92)	0.057
COPD	46 (5.86)	8 (4.67)	38 (6.19)	0.071
Cancer	35 (4.46)	10 (5.85)	25 (4.08)	0.184
Others	153 (19.49)	25 (14.62)	128 (20.85)	0.079
Weight, kg	64.28 ± 14.91	64.53 ± 11.28	63.94 ± 13.37	0.156
Height, m	1.65 ± 0.12	1.63 ± 0.14	1.67 ± 0.15	0.284
BMI	24.59 ± 4.57	24.31 ± 4.22	24.84 ± 4.68	0.489
HD frequency	-	-	-	0.063
2 times a week	223 (28.41)	62 (36.25)	161 (26.22)	
3 times a week	557 (70.95)	108 (63.16)	449 (73.12)	
4 times a week	5 (0.64)	1 (0.61)	4 (0.58)	
Dialyzer	-	-	-	0.098
High Flux	489 (62.29)	96 (56.14)	393 (64.01)	
Low Flux	291 (37.07)	74 (43.27)	217 (35.34)	
Others	5 (0.64)	1 (0.63)	4 (0.65)	
BP Control	-	-	-	-
ACE/ARB	604 (76.94)	130 (76.02)	474 (77.19)	0.438
Beta-block	430 (54.77)	96 (56.14)	334 (54.40)	0.633
Calcium block	424 (54.01)	89 (52.05)	335 (54.56)	0.245
Alpha	147 (18.73)	30 (17.54)	117 (19.06)	0.132
Diuretic	67 (8.53)	23 (13.45)	44 (7.17)	**0.024**
Others	76 (9.68)	15 (8.77)	61 (9.93)	0.51
Other medications	-	-	-	-
Iron	498 (63.44)	107 (62.57)	391 (63.68)	0.771
Calcium	408 (51.97)	77 (45.02)	331 (53.91)	**0.037**
Sevelamer	349 (44.46)	56 (32.75)	293 (47.72)	**0.001**
Clopidogrel	268 (34.14)	52 (30.41)	216 (35.18)	0.141
Aspirin	157 (20.00)	32 (18.71)	125 (20.36)	0.672
Insulin	99 (12.61)	31 (18.90)	68 (11.07)	**0.025**
Calcitriol	94 (11.97)	20 (11.69)	74 (12.05)	0.704
DPP-4	77 (9.81)	14 (8.19)	63 (10.26)	0.146
SU	22 (2.80)	5 (2.92)	17 (2.76)	0.591
Lipid Lowering	-	-	-	-
Statin	398 (50.70)	84 (49.12)	314 (51.14)	0.568
Fibrates	28 (3.56)	7 (4.09)	21 (3.42)	0.607
Nicotinamide	4 (0.51)	0	4 (0.65)	0.175
Epoetin	-	-	-	-
Alfa	381 (48.53)	64 (37.43)	317 (51.14)	**0.006**
Beta	322 (41.02)	70 (40.93)	252 (41.04)	-
Darbepoetin	12 (1.53)	4 (2.34)	8 (1.30)	-
PEG	4 (0.51)	2 (1.17)	2 (0.33)	-
None	66 (8.41)	31 (18.13)	35 (5.70)	-
Epoetin dose, weekly	12000 (8000 to 12000)	12000 (8000 to 15000)	12000 (8000 to 12000)	0.145
Symptoms	-	-	-	-
Cough	522 (66.50)	123 (71.93)	399 (64.98)	0.083
DOB	498 (63.44)	118 (69.01)	380 (61.89)	**0.026**
Fever	440 (56.05)	96 (56.14)	344 (56.03)	0.847
Neuro	71 (9.04)	12 (7.02)	59 (9.61)	0.482
Gastro	58 (7.39)	12 (7.02)	46 (7.49)	0.903
Other symptoms	199 (25.35)	32 (18.71)	167 (27.19)	0.072

Table 3. Baseline lab values of adult HD patients who developed COVID.

-	Total (n=735)	Died (n=164, 22%)	Survived (n=571, 78%)	-
	Median (IQR)			
Hematologic parameters	-	-	-	-
Hemoglobin	10.38 (9 to 12)	10.74 (9.5 to 12.75)	10.2 (8.9 to 11.6)	**0.028**
WBC	7.3 (5 to 10.3)	7.54 (5 to 11.5)	7.23 (5 to 9.99)	0.812
Eosinophil	1 (0 to 3)	1 (0 to 3)	1 (0 to 4)	**0.003**
Hematocrit	0.30 (0.27 to 0.35)	0.35 (0.28 to 0.38)	0.29 (0.27 to 0.34)	**0.026**
Neutrophil	77 (64 to 88)	80 (72 to 87)	75 (65 to 83)	**<0.001**
Basophil	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.060
Lymph	14 (8 to 21)	12 (5 to 21.5)	15 (10 to 21)	**0.017**
Platelet	195 (152 to 241)	176 (138 to 231)	201 (154 to 261)	**0.011**
Electrolytes	-	-	-	-
Sodium	136 (132 to 139)	136 (132 to 139)	136 (133 to 141)	0.219
Potassium	4.5 (3.8 to 5.4)	4.7 (4.0 to 5.4)	4.5 (3.8 to 5.3)	**0.037**
Chloride	100 (93 to 105)	99 (93 to 102)	102 (97 to 105)	**0.017**
Mg	1.21 (0.9 to 1.8)	1.13 (0.91 to 1.76)	1.27 (0.9 to 1.8)	0.310
Ionized Ca	1.11 (1 to 1.2)	1.07 (0.99 to 1.2)	1.12 (1 to 1.2)	0.601
Total Ca	2.13 (1.75 to 2.45)	1.95 (1.7 to 2.16)	2.27 (2 to 2.45)	**<0.001**
Albumin	3.16 (2.7 to 3.7)	3 (2.7 to 3.4)	3.2 (2.8 to 3.8)	**0.004**
ABG	-	-	-	-
pH	7.39 (7.31 to 7.46)	7.36 (7.25 to 7.42)	7.39 (7.32 to 7.48)	**0.014**
pCO2	32.95 (28 to 38)	32.12 (26.5 to 38)	33.07 (29 to 38.5)	0.187
pO2	90 (65 to 105)	78 (62 to 98)	96 (73.5 to 105)	**0.016**
HCO3	19.43 (16 to 24)	17.23 (13 to 23.5)	20.2 (16.5 to 23.5)	**0.009**
AG	17 (13 to 21.4)	19 (13 to 22)	16.1 (13 to 21)	0.094
O2 Sat	97 (93 to 98)	96 (92 to 98)	97 (94 to 98)	**0.002**
PaO2/FiO2	288 (159 to 417)	173 (116 to 281)	332 (227 to 460)	**<0.001**
Biomarkers done	-	-	-	-
CRP	25.2 (9.8 to 47.9)	32.6 (12.2 to 56.7)	23.1 (8.7 to 45)	**0.030**
D-dimer	1.7 (0.7 to 2.3)	1.9 (1.2 to 3.1)	1.6 (0.6 to 2.3)	**0.008**
Ferritin	423 (219 to 613)	529 (316 to 687)	352 (198 to 564)	**<0.001**
LDH	301 (186 to 490)	379 (219 to 589)	269 (179 to 424)	**<0.001**
Procalcitonin	3.2 (1.6 to 5.6)	4.9 (2.6 to 7.3)	2.5 (1.2 to 4.8)	**<0.001**
ESR	39 (26 to 54)	48 (35 to 64)	35 (23 to 49)	**<0.001**

Also, in Table 1, results show a large proportion of patients in survivor and mortality groups have hemodialysis sessions three times a week. Most of them use a high-flux dialyzer, but there was no statistical difference among the groups. Among the initial symptoms, cough is the most common symptom, experienced by two-thirds of the subjects, followed by dyspnea and fever. On analysis, only dyspnea was significantly higher among mortalities than survivors.

Based on the initial laboratory determinations (Table 3), those who died surprisingly had a higher baseline hemoglobin/ hematocrit and neutrophils, with lower eosinophils, lymphocyte, and platelet counts in Complete Blood Count (CBC). In terms of electrolytes, non-survivors had a higher baseline serum potassium and lower serum chloride and calcium. Arterial blood analysis showed lower pH, pO2, PaO2/FiO2 ratio, and serum bicarbonate values among mortalities. As expected, those who died also had higher baseline inflammatory markers. The rest of the laboratory parameters were not statistically significant.

In terms of clinical course (Table 4), there was a significantly higher proportion of patients in the mortality group who developed cytokine storm, sepsis, and septic shock. Overall, a quarter of all patients needed ICU admission, with most of the patients in the mortality group. However, ICU days between survivors and non-survivors were not statistically significant. The rest of the patients were admitted to the COVID area and home quarantine. 43% of patients received remdesivir, with a significantly higher proportion in the mortality group. Similar trends were noted in dexamethasone, tocilizumab, and hydrocortisone. 43% of patients also received anti-coagulation for prophylaxis, but still with a significantly higher proportion in the mortality group. There is also a higher mortality in those given anti-coagulation for extracorporeal treatment.

Almost 80% did not require inotropes, and those who required such intervention also had a significantly higher proportion in the mortality group. There is also less mortality among those who do not require or need minimal supplementary oxygen. In terms of hemodialysis prescription, more than two-thirds of patients did not require modification. For those who shifted to SLED, CVVHDF, or increased frequency, the percentage was significantly higher for the mortality. Almost 13% of patients also had hemoperfusion, and while the proportion favored the survivor group, a significantly higher percentage of patients in the mortality group underwent the procedure. A small percentage (2.92%) had convalescent plasma therapy. In terms of mechanical ventilatory days and length of hospital stay, there is no statistical difference between the two groups.

Table 4. Clinical outcomes of adult HD patients who developed COVID.

-	Total (n=785)	Died (n=171, 22%)	Survived (n=614, 78%)	-
	Frequency (%); Median (IQR)			
Cytokine Storm	256 (32.61)	123 (71.93)	133 (21.66)	**<0.001**
Sepsis	279 (35.54)	136 (79.53)	143 (23.29)	**<0.001**
Septic Shock	146 (18.60)	115 (67.25)	30 (4.89)	**<0.001**
Location	-	-	-	**<0.001**
Ward	438 (55.80)	56 (32.74)	382 (62.21)	
ICU	196 (24.97)	115 (67.25)	81 (13.19)	
Home	151 (19.23)	0	151 (24.60)	
ICU Days	7 (5 to 12)	6 (4 to 11)	9 (5 to 13)	0.067
Remdesivir	338 (43.06)	94 (54.97)	221 (39.73)	**<0.001**
Immuno-Modulator	-	-	-	-
Dexamethasone	390 (49.68)	121 (70.76)	269 (43.81)	**<0.001**
Tocilizumab	102 (12.99)	49 (28.65)	53 (8.63)	**<0.001**
Hydrocortisone	49 (6.24)	12 (7.32)	33 (5.37)	**<0.001**
Others	19 (2.59)	1 (0.61)	18 (3.15)	0.092
Use of Anti-Coagulant	-	-	-	-
Prophylaxis	341 (43.44)	123 (71.92)	218 (35.50)	**<0.001**
Extracorporeal circuit	125 (15.92)	40 (23.39)	85 (13.84)	**0.004**
Thrombosis treatment	38 (4.84)	8 (4.67)	30 (4.89)	1
Number of inotropes	-	-	-	**<0.001**
0	624 (79.49)	69 (40.35)	555 (90.39)	
1	55 (7.01)	30 (17.54)	25 (4.07)	
2	46 (5.86)	26 (15.20)	20 (3.25)	
3	60 (7.64)	46 (26.90)	14 (2.28)	
Respiratory Support	-	-	-	**<0.001**
None	285 (36.31)	6 (3.51)	279 (45.44)	
Regular O2	276 (35.17)	31 (18.12)	245 (39.90)	
HFNC	89 (11.33)	32 (18.71)	57 (9.28)	
Mechanical ventilation	135 (17.19)	102 (59.66)	33 (5.38)	
Duration of mechanical ventilation	6 (3 to 10)	6 (2 to 10)	6 (3 to 7)	0.827
Dialysis Modification	-	-	-	**<0.001**
None	526 (67.01)	75 (43.86)	451 (89.89)	
Increased Frequency	110 (14.01)	23 (13.46)	87 (5.68)	
SLED	103 (13.12)	56 (32.74)	57 (7.26)	
CVVHDF	44 (5.61)	15 (8.77)	29 (4.72)	
PIRRT	2 (0.25)	2 (1.17)	0	
Heparinization	-	-	-	**0.004**
Low Dose	262 (33.38)	61 (35.67)	201 (32.74)	
LMWH	205 (26.12)	59 (34.50)	146 (23.78)	
Regular	163 (20.76)	23 (13.45)	140 (22.80)	
Heparin Free	155 (19.74)	28 (16.38)	127 (20.68)	
Hemoperfusion	104 (12.95)	43 (25.15)	61 (9.93)	**<0.001**
Convalescent Plasma	23 (2.92)	8 (4.67)	15 (2.44)	0.125
Length of hospital stay	11 (5 to 19)	10 (5 to 19)	12 (7 to 20)	0.31

A summary of all significant factors is enumerated in Table 5 using univariate analysis. On multivariate analysis (Table 6), only five factors were found to be significant independent of other factors. These are the presence of cytokine storm, sepsis, use of heparin for extracorporeal therapy, use of tocilizumab, and elevated D-dimer values.

Table 5. Factors associated with mortality (univariate).

Parameters	Crude odds ratio	95% CI	*p*-value
Hypertension as comorbidity	1.6762	1.0621 to 2.6455	**0.031**
Diuretic	1.9248	1.0234 to 3.6200	**0.024**
Sevelamer	0.5591	0.3832 to 0.8156	**0.037**
Insulin	1.7906	1.0849 to 2.9556	**0.025**
Difficulty of breathing	2.4525	1.6786 to 3.5833	**0.026**
Hematocrit (100)	1.054	1.0291 to 1.0794	**<0.001**
Neutrophil	1.038	1.0205 to 1.0557	**<0.001**
Platelet	0.9973	0.9950 to 0.9997	**0.025**
Potassium	1.2308	1.0211 to 1.4936	**0.029**
Chloride	0.9582	0.9192 to 0.9989	**0.044**
Total Ca	0.7284	0.5567 to 0.9530	**0.021**
Albumin	0.6115	0.4342 to 0.8613	**0.005**
pH	0.0469	0.0070 to 0.3158	**0.002**
pO2	0.9942	0.9890 to 0.9995	**0.031**
PaO2/FiO2	0.9939	0.9923 to 0.9956	**<0.001**
CRP	1.0068	1.0005 to 1.0131	**0.033**
D-dimer	1.3402	1.1084 to 1.6206	**0.003**
Ferritin	1.002	1.0012 to 1.0029	**<0.001**
LDH	1.0015	1.0006 to 1.0024	**0.002**
Procalcitonin	1.2324	1.1308 to 1.3432	**<0.001**
ESR	1.0287	1.0119 to 1.0457	**0.001**
Cytokine Storm	8.3222	5.5556 to 12.466	**<0.001**
Sepsis	12.543	8.1087 to 19.403	**<0.001**
Septic Shock	40.487	23.443 to 69.920	**<0.001**
Location	-	-	-
Ward	24.261	3.3189 to 177.34	**0.002**
ICU	221.63	30.215 to 1625.8	**<0.001**
Home	(reference)	-	-
Remdesivir	2.4637	1.7067 to 3.5563	**<0.001**
Immuno-Modulator	-	-	-
Dexamethasone	3.7741	2.5424 to 5.6024	**<0.001**
Tocilizumab	4.705	2.8921 to 7.6545	**<0.001**
Hydrocortisone	2.921	1.3041 to 6.5423	**0.009**
Use of Anti-Coagulant	-	-	-
Prophylaxis	3.7092	2.4990 to 5.5055	**<0.001**
Extracorporeal circuit	1.8265	1.1485 to 2.9047	**0.011**
Number of inotropes	5.4369	3.9021 to 7.5753	**<0.001**
Respiratory Support	-	-	-
None	(reference)	-	**-**
Regular O2	5.25	2.1395 to 12.883	**<0.001**
HFNC	21.163	8.2143 to 54.523	**<0.001**
Mechanical ventilation	152.72	59.99 to 388.81	**<0.001**
Hemoperfusion	4.1802	2.5876 to 6.7530	**<0.001**

Table 6. Factors associated with mortality (multivariate).

Parameters	Adjusted Odds Ratio	95% CI	*p*-value
Cytokine Storm	4.9469	1.7201 to 14.227	**0.003**
Sepsis	3.9026	1.4599 to 10.432	**0.007**
Extracorporeal circuit	7.6346	2.0170 to 28.897	**0.003**
Tocilizumab	3.4299	1.3651 to 8.6177	**0.009**
D-dimer	1.4949	1.0743 to 2.0802	**0.017**

4. DISCUSSION

In our study, the prevalence of COVID among hemodialysis patients in PSN-accredited training institutions is 5.1%. Variations exist depending on the country, area, or center/s covered. The prevalence in the study is slightly higher than the initial study in Wuhan, China, of 2.2% [15]. However, this was lower in another study in a hemodialysis center in Wuhan, which was 11% [15]. The highest prevalence of COVID among hemodialysis patients was in two centers in the United Kingdom, with a combined 22.2% prevalence of asymptomatic patients using serologic screening [16].

Locally, there are two major studies published before this. The first one was a retrospective, observational study of 68 COVID-positive hemodialysis patients in the University of the Philippines-Philippine General Hospital (PGH) [17]. Prevalence was not determined, and the study period lasted for 4 months during the start of the pandemic. The second was performed in the National Kidney and Transplant Institute (NKTI), involving not just hemodialysis patients but also peritoneal dialysis patients and those initiated on renal replacement therapy. 68% of the subjects were hemodialysis patients infected with COVID [18].

This study was performed in more centers than in the previous studies mentioned. Results showed that the mean age of subjects is more than 60 years old, the majority were males, with diabetes as the primary cause of CKD, on hemodialysis for an average of 2 years, and hypertension as the most common and significant co-morbidity, followed by diabetes and dyslipidemia. The patients in the PGH were younger average-wise and hypertension was the most common cause of CKD. Study characteristics in this study are almost similar to the NKTI study, albeit a younger age in the latter and lesser duration of dialysis (a mean of 1 year). Cough was the most common symptom in this study, followed by dyspnea and fever. However, dyspnea was the only significantly higher percentage among those who died compared to survivors. The studies from PGH and NKTI have dyspnea as its most common symptom.

In terms of laboratories, non-survivors surprisingly have higher hemoglobin, hematocrit, and neutrophil values, with lower lymphocyte and platelet counts. This is different from the PGH study, in which the only significant hematologic parameter was a higher WBC among mortalities. In terms of electrolytes, the mortalities also had significantly higher serum potassium levels despite no recorded hyperkalemia (Serum K >6 mmol/l) and lower calcium and chloride. Hypochloremia and hypocalcemia were found to be associated with poor outcomes in COVID-19 hospitalized patients in other studies [19, 20]. This is likely since these imbalances can worsen the effects of the virus on the body. For example, hypocalcemia can weaken the heart and make it more difficult for the body to fight off infection. Hypochloremia can also worsen respiratory symptoms, as chloride is important for the function of the lungs [20].

Among the biomarkers, non-survivors also had significantly higher LDH and procalcitonin levels. These trends were also noted in the same studies. High LDH levels indicate increased cell damage and damage to muscles [21]. Procalcitonin levels are also significantly higher among mortalities. This protein, produced primarily by the thyroid gland and white blood cells, is also an inflammatory marker. It can indicate direct damage to the lungs because of the infection [21]. Unique to this study is that other markers were also elevated in mortalities. D-dimer is significantly higher, which is a protein fragment produced when fibrin clots dissolve. It is elevated in conditions that cause blood clots, like pulmonary embolism and deep venous thrombosis. COVID-19 is a pro-thrombotic disease, and this could mean that thrombi formation and possibly a contributory cause of death among these patients despite the use of anti-coagulation. C-Reactive Protein, Ferritin, and ESR were also elevated, indicative of a high inflammatory state of COVID patients with unfavorable outcomes.

There are still variations in terms of the management of these patients. Since the two local studies were performed early in the pandemic, Azithromycin and Hydroxy-chloroquine were the most common medications given in the PGH study, while Tocilizumab and Hydroxychloroquine were given in the NKTI study. For this study, almost half of the patients were given Dexamethasone, followed by Remdesivir. A significantly higher proportion though, was noted among those who died, which reflects that most of these patients have severe presentations that warranted the use of these medications. There was a small percentage of patients given Tocilizumab and other steroids like Hydrocortisone. This study also determined the use of inotropes among patients. While most patients did not require inotropes, those who required at least one most likely have an unfavorable outcome.

An advantage of this study was that it classified patients with unfavorable complications. About a third of all patients developed cytokine storm and sepsis, while more than 18% developed septic shock. A significantly higher proportion of these patients were in the mortality group, consistent with the premise that disease severity portends poorer outcomes. Also, 17% of patients required mechanical ventilation, as in the PGH study, and this is a significant factor in mortality.

Another unique outcome of the study was it determine if there were modifications with the hemodialysis prescription or if other extracorporeal therapies were performed. The majority of the patients did not require any modification to their usual treatment. For those with increased frequency, who used SLED and even CRRT, a significantly higher percentage of patients were in the mortality group, reflecting the severe effect of the infection. Hemoperfusion was performed in 13% of patients, slightly more than in the PGH and NKTI studies, and more patients who underwent convalescent plasma therapy.

In terms of multivariate analysis, five factors were found to be independently associated with mortality. Presence of sepsis and cytokine storm is correlated with mortality among COVID-19 dialysis patients [22, 23]. Cytokine storm refers to an excessive and uncontrolled release of pro-inflammatory cytokines that leads to severe inflammation, organ damage, and poor outcomes. It also leads to sepsis, causing organ dysfunction. Hence, therapies targeting pathways of minimizing cytokine production were investigated in these patients [23]. One of these is Tocilizumab, which is a humanized monoclonal antibody that binds to the interleukin-6 (IL-6) receptor. IL-6 is a cytokine that plays a role in inflammation and immune responses. Tocilizumab blocks the binding of IL-6 to its receptor, which prevents IL-6 from activating its downstream signaling pathways. This leads to a reduction in inflammation and immune responses [24]. However, there are still conflicting results as to its efficacy. In a study conducted in nine hospitals in Brazil, a randomized controlled trial was performed by giving Tocilizumab to some patients. Adverse events and need for mechanical ventilation were not different from standard care alone, and there was even a higher percentage of death in the treatment group, albeit not statistically significant [25]. On the other hand, a study by Eskazan and colleagues showed that mortality was lower among patients given tocilizumab [26]. Further investigations must be performed to establish its efficacy and also look at other factors such as timing of administration and patient sub-groups.

Use of an anti-coagulant for extracorporeal therapy was another independent factor. This could be related to the fifth factor, which is elevated D-dimer. Studies have highlighted that anti-coagulant use in COVID-19 patients is due to the prothrombotic state induced by the virus, causing endothelial dysfunction [27]. As mentioned, an elevated D-dimer is related to thrombotic episodes. Use of this drug has been associated with improved survival in critically ill COVID-19 patients by either preventing or lysing any blood clots present [28]. However, it is possible that timing of administration, heavy thrombi load, and interaction with other medications can affect the efficacy of anti-coagulants among the mortalities. These independent factors were different from the PGH study, where patients who needed mechanical ventilators, elevated procalcitonin, and a low PaO2/ FiO2 ratio were noted.

The initial plan of this study was also to analyze COVID infections among peritoneal dialysis patients. However, we only collected four patients, which is far below the minimum sample size. A possible recommendation is to continue data collection until the required number of subjects is reached. However, the data for hemodialysis is one of the largest numbers of subjects involved. The only two published studies with larger samples to date were the ERACODA study, which was an initiative of the European Renal Association-European Dialysis Transplant Association with 1141 subjects [29], and the study investigating dialysis attributes and strategies with COVID cases in London, with about 990 confirmed cases [30].

It could be possible that sub-group analysis can be performed, and the investigators will investigate this possibility. Another recommendation would be randomized controlled trials on different management aspects, from various drugs to the use of hemoperfusion or convalescent plasma. Since it can be assumed that the management of these patients is better due to the monitoring of both Nephrologists, Nephrologists-in-Training, and other Specialists, looking at clinical characteristics and outcomes of COVID-19 hemodialysis patients in hospitals without Nephrology Fellowship Training can be investigated.

CONCLUSION

This study has demonstrated one of the more susceptible groups of individuals that was affected by COVID-19, affecting more than 5% of hemodialysis patients. Mostly, it has similar clinical characteristics, management, and outcomes to other studies of this kind. Hemodialysis patients with COVID-19 infection presenting with sepsis, cytokine storm, and thrombotic episodes should be considered as high risk for unfavorable outcomes, and timely interventions must be done to minimize death in these individuals.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: R.B.: Study conception and design; Analysis and interpretation of results; Draft Manuscript; R.F.: Study conception and design; A.C.: Study conception and design; J.C.C.N.: Validation; A.A.: Draft manuscript editing. J.M.Z.: Data collection; A.M.: Data collection; J.R.E.: Data collection; C.Q.: Data collection; K.C.: Data collection; A.C.: Data collection; B.M.C.: Data collection; A.R.V.: Data collection; B.L.L.: Data collection; M.A.: Data collection; M.R.U.: Data collection; M.L.: Data collection; M.S.: Data collection; J.J.M.: Data collection; V.V.: Data collection; R.M.: Data collection; J.I.L.: Data collection; M.E.L.: Data collection; C.H.T.: Data collection; R.N.M.: Data collection; A.P.A.: Data collection; A.M.R.: Data collection; M.N.: Data collection; V.J.B.: Data collection. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

HD = Hemodialysis

PD = Peritoneal Dialysis

PCR = Polymerase Chain Reaction

DCF	=	Data Collection Form
ICU	=	Intensive Care Unit
CKD	=	Chronic Kidney Disease
CBC	=	Complete Blood Count
SLED	=	Sustained Low-Efficiency Dialysis
CVVHDF	=	Continuous Venovenous Hemodiafiltration
CRRT	=	Continuous Renal Replacement Therapy
LDH	=	Lactate Dehydrogenase

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

An application for single joint research ethics board (SJREB) approval from the Department of Health was also submitted and approved (Approval Number SJREB 2022-012).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article will be available from the corresponding author [R.B.] upon reasonable request.

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CONFLICT OF INTEREST

The author(s) declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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