ORIGINAL ARTICLE

Predictors of Mortality among End-Stage Renal Disease Patients with COVID-19 Admitted in a Philippine Tertiary Government Hospital: A Retrospective Cohort Study

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ABSTRACT

Background and Objective. Several studies have examined the predictors of mortality among COVID-19-infected patients; however, to date, few published studies focused on end-stage renal disease patients. The present study, therefore, aims to determine the predictors of in-hospital mortality among end-stage renal disease patients with COVID-19 admitted to a Philippine tertiary hospital.

Methods. The researcher utilized a retrospective cohort design. A total of 449 adult end-stage renal disease patients on renal replacement therapy diagnosed with moderate-to-severe COVID-19 and were admitted at the National Kidney and Transplant Institute from June 2020 to 2021 were included. Logistic regression analysis was used to determine the factors associated with in-hospital mortality.

Results. In-hospital mortality among end-stage renal disease patients with COVID-19 was 31.18% (95% CI: 26.92-35.69%). Older age (OR=1.03), male sex (OR=0.56), diabetes mellitus (OR=1.80), coronary artery disease (OR=1.71), encephalopathy (OR=7.58), and intubation (OR=30.78) were associated with in-hospital mortality.

Conclusion. Patients with ESRD and COVID-19 showed a high in-hospital mortality rate. Older age, diabetes mellitus, coronary artery disease, encephalopathy, and intubation increased the odds of mortality. Meanwhile, males had lower odds of mortality than females.

Keywords: COVID-19, end-stage renal disease, in-hospital mortality, renal replacement therapy

INTRODUCTION

By the end of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread across countries, creating the COVID-19 pandemic. Although the number of new cases is decreasing due to the availability of vaccines, transmission is still ongoing, and its end remains uncertain. As of May 2023, the World Health Organization recorded over 700 million confirmed cases and 7 million deaths.[1]

While most cases of COVID-19 were asymptomatic and mild, the elderly and individuals with comorbidities are considered vulnerable to more severe infection and poorer outcomes. Most end-stage renal disease (ESRD) patients are older and have various comorbidities, so this population is known to be vulnerable to COVID-19 infection. Patients with chronic kidney disease (CKD) had four times higher odds of mortality due to COVID-19 compared to those without

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CKD based on a recent meta-analysis.[2] Furthermore, those on renal replacement therapy (RRT) had a higher likelihood of infection, complications, and death due to their poorer immune status.[3–7] Published studies reported in-hospital mortality rate among ESRD patients as high as 38%.[6–18]

The current number of active RRT patients in the Philippines is unknown. Nevertheless, based on a meta-analysis of low- and middle-income countries, the Philippines is the leading country in the CKD prevalence. Based on this study, the pooled prevalence of CKD stage 3-5 is 35.94% compared to <20% in other LMICs.[19] Studies focusing on ESRD have remained limited for over three years since the COVID-19 pandemic started, especially in the local setting. Given the high burden of CKD in the Philippines, a better understanding of the outcomes of these patients when infected with COVID-19 is warranted. Therefore, the present study aims to determine the predictors of in-hospital mortality among ESRD patients with COVID-19 admitted at the National Kidney and Transplant Institute (NKTI), the specialty center for treating renal disease, dialysis, and organ transplantation in the country.

METHODS

The researcher utilized a retrospective cohort design. All eligible ESRD patients on RRT diagnosed with COVID-19 and admitted at NKTI from June 1, 2020 to June 30, 2021 were included in the study. The study included adults aged 18 years, clinically diagnosed with ESRD, currently undergoing RRT, confirmed to have moderate-to-severe COVID-19 thru RT-PCR or COVID GeneXpert, and have complete data for all variables. Those patients who did not have RT-PCR/ COVID GeneXpert results were excluded.

PASS 2021 software was used to calculate the sample size required. A minimum of 230 ESRD patients with COVID-19 are needed to achieve 90% statistical power using multiple logistic regression analysis with at most 30 factors specifying a medium effect size (Cohen's f=0.15) and alpha set at 0.05. Although a minimum sample size was presented, the researcher opted to conduct total enumeration wherein all eligible patients were included in the study.

Before the conduct of the study, approval was obtained from the NKTI Research Ethics Committee (Protocol No. 2020-87). Data gathering was performed from July 15 to August 15, 2021. Medical charts were retrieved, and the following variables were collected: age, sex, comorbidities, vital signs [heart rate, respiratory rate, oxygen saturation, systolic blood pressure (SBP), diastolic blood pressure (DBP), and highest temperature], RRT [hemodialysis (HD), peritoneal dialysis (PD) or both], and COVID-19 management performed. The outcome of interest was in-hospital mortality, defined as death due to any cause during the hospital stay. The operational definition of variables is provided in Appendix A. The study flow diagram for this study is presented in Appendix B.

Stata MP version 17 software was used for the data processing and analysis. Continuous variables were presented as median (interquartile range/IQR) due to the non-normal data distribution. Categorical variables were expressed as frequencies and percentages. Mann Whitney U test was used to compare continuous variables, while Chi-Square test and Fisher's Exact test were used for categorical variables. In order to determine the factors associated with in-hospital mortality, logistic regression analysis was performed. Potential factors were screened using simple logistic regression based on the $p<0.20$ criteria.[20] Model building was done using multiple logistic regression with a backward elimination technique. Missing values were neither replaced nor imputed. P values ≤ 0.05 were considered statistically significant.

RESULTS

A total of 501 ESRD patients with COVID-19 were identified from the medical records. Fifty-two were excluded due to incomplete data; 449 patients were eventually included in the study. The in-hospital mortality rate was 31.18% (95% CI: 26.92-35.69%).

Table 1 presents the characteristics of the included patients. The median age was 53, ranging from 19 to 92 years old. Most were males, and the most common comorbidity was hypertension. The median age of patients who died was significantly higher than those who survived. A higher proportion of patients with hypertension, diabetes mellitus, coronary artery disease, stroke, and encephalopathy died than those without these comorbidities (all p's ≤ 0.05).

Table 2 presents the vital signs on admission of the patients. Vital signs were primarily normal except for systolic blood pressure, wherein more than half had high values. In-hospital mortality rates significantly differ by diastolic blood pressure (DBP) level. Most patients (66%) with low DBP died compared to only 33% and 23% of patients with normal and high DBP, respectively.

Table 3 shows the management performed on the patients during hospital admission. Among all the management for COVID-19 available, most received azithromycin (62%) and dexamethasone (66%). The majority of the patients underwent HD only. Only about a fifth of the patients underwent intubation, and 5% were admitted to the intensive care unit (ICU). A higher proportion of patients who received azithromycin, dexamethasone, and hemoperfusion died than those who did not receive the said treatment modalities. Mortality rates also differ by RRT modality. More than a third of patients who underwent HD died compared to 27% of those who underwent HD and PD and 10% of those who underwent PD only. Patients who underwent intubation and were admitted to ICU were also more likely to die than those who did not.

Table 1. Characteristics of COVID-19 ESRD Patients on RRT (n=449)

Demographic	All patients	Died	Survived	*P* value
Age (in years), median	53 [IQR: 40-62]	57 [IQR: 50-87]	50 [IQR: 38-61]	<0.00001*
Sex				
Female	188 (42)	66 (35)	122 (65)	0.148
Male	261 (58)	74 (28)	187 (72)	
Comorbidities	**All patients**	**Died**	**Survived**	***P* value**
Hypertension				
With	339 (76)	115 (34)	224 (66)	0.028*
Without	110 (24)	25 (23)	85 (77)	
Diabetes mellitus				
With	186 (41)	78 (42)	108 (58)	<0.0001*
Without	263 (59)	62 (24)	201 (76)	
Coronary artery disease				
With	182 (41)	75 (41)	107 (59)	<0.0001*
Without	267 (59)	65 (24)	202 (76)	
Heart failure				
With	79 (18)	23 (29)	56 (71)	0.662
Without	370 (82)	117 (32)	253 (82)	
Other cardiac disease				
With	35 (8)	11 (31)	24 (69)	0.974
Without	414 (92)	129 (31)	285 (69)	
Asthma				
With	11 (2)	2 (18)	9 (82)	0.515
Without	438 (98)	138 (32)	300 (68)	
COPD				
With	15 (3)	8 (53)	7 (47)	0.085
Without	434 (97)	132 (30)	302 (70)	
OSA				
With	4 (1)	1 (25)	3 (75)	1.000
Without	445 (99)	139 (31)	306 (69)	
PTB				
With	46 (10)	18 (39)	28 (61)	0.219
Without	403 (90)	122 (30)	281 (70)	
Stroke				
With	51 (11)	25 (49)	26 (51)	0.003*
Without	398 (89)	115 (29)	283 (71)	
Seizure				
With	17 (4)	7 (41)	10 (59)	0.364
Without	432 (96)	133 (31)	299 (69)	
Encephalopathy				
With	25 (6)	16 (64)	9 (36)	<0.0001*
Without	424 (96)	124 (29)	300 (71)	
Other neurologic disease				
With	4 (1)	1 (25)	3 (75)	1.000
Without	445 (99)	139 (31)	306 (69)	
Other disease				
With	3 (1)	1 (33)	2 (67)	1.000
Without	446 (99)	139 (31)	307 (69)	

Table 2. Vital Signs on Admission of COVID-19 ESRD Patients on RRT (n=449)

	All patients	Died	Survived	*P* value
Heart rate				
Normal	343 (76)	112 (33)	231 (67)	0.236
Low	5 (1)	0	5 (100)	
High	101 (22)	28 (28)	73 (72)	
Respiratory rate				
Normal	291 (65)	84 (29)	207 (71)	0.151
High	158 (35)	56 (35)	102 (65)	
Oxygen saturation				
Normal	333 (74)	98 (29)	235 (71)	0.175
Abnormal	116 (26)	42 (36)	74 (64)	
Systolic blood pressure				
Normal	177 (39)	60 (34)	117 (66)	0.057
Low	41 (9)	18 (44)	23 (56)	
High	231 (51)	62 (27)	169 (73)	
Diastolic blood pressure				
Normal	273 (61)	90 (33)	183 (67)	0.001*
Low	27 (6)	16 (59)	11 (41)	
High	149 (33)	34 (23)	115 (77)	
Highest temperature				
Normal	326 (73)	98 (30)	228 (70)	0.405
Fever	123 (27)	42 (34)	81 (66)	

Table 3. Management of COVID-19 ESRD Patients on RRT (n=449)

Treatment received	All patients	Died	Survived	*P* value
Azithromycin				
Yes	278 (62)	100 (36)	178 (64)	0.005*
No	171 (38)	40 (23)	131 (77)	
Tocilizumab				
Yes	21 (5)	10 (48)	11 (52)	0.096
No	428 (95)	130 (30)	298 (70)	
Remdesivir				
Yes	7 (2)	4 (57)	3 (43)	0.212
No	442 (98)	136 (31)	306 (69)	
Dexamethasone				
Yes	295 (66)	105 (36)	190 (64)	0.005*
No	154 (34)	35 (23)	119 (77)	
Hemoperfusion				
Yes	50 (11)	22 (44)	28 (56)	0.038*
No	399 (89)	118 (30)	70	
RRT				
HD only	353 (79)	125 (35)	228 (65)	<0.0001*
PD only	63 (14)	6 (10)	57 (90)	
HD and PD	33 (7)	9 (27)	24 (73)	
Intubation				
Yes	87 (19)	74 (85)	13 (15)	<0.0001*
No	362 (81)	66 (18)	296 (82)	
ICU admission				
Yes	22 (5)	17 (77)	5 (23)	<0.0001*
No	427 (95)	123 (29)	304 (71)	

Table 4. Factors Associated with In-hospital Mortality among COVID-19 ESRD Patients on RRT (n=449)

	Adjusted OR (95% CI)	*P* value
Age	1.03 (1.01-1.05)	0.002*
Sex		
Female	Ref	Ref
Male	0.56 (0.33-0.95)	0.032*
Comorbidities (Ref: Without)		
DM	1.80 (1.04-3.11)	0.036*
CAD	1.71 (1.01-2.92)	0.050*
Encephalopathy	7.58 (2.79-20.58)	<0.0001*
Intubation	30.78 (15.21-62.27)	<0.0001*

Univariable analysis showed several variables which were significantly associated with in-hospital mortality (Appendix C). Higher odds of mortality were observed among patients with increasing age, hypertension, DM, CAD, stroke, encephalopathy, azithromycin use, dexamethasone, hemoperfusion, intubation, and ICU admission (all p's ≤0.05). Meanwhile, compared to normal DBP, low DBP increases the odds of mortality, while high DBP decreases it. Patients who underwent PD had lower odds of mortality than those who underwent HD.

Table 4 presents the final set of predictors associated with in-hospital mortality. For every year increase in age, the odds of mortality increase by 3%. Males were two times less likely to die than females. Meanwhile, only DM, CAD, and encephalopathy increase the odds of in-hospital mortality across all comorbidities. Intubated patients also have higher odds of death than those who were not.

DISCUSSION

ESRD patients are vulnerable to COVID-19, and outcomes were much poorer in this group. However, to date, only one published local study focuses on dialysis patients infected with COVID-19.[21] The study by Tomacruz et al. was performed in the Philippine General Hospital with 68 patients admitted from April to July 2020.[21] Meanwhile, the current study was performed in the NKTI, the country's specialty center for renal disease. With 449 cases included since the start of the pandemic, this large retrospective cohort study provides valuable information on the factors associated with in-hospital mortality among ESRD patients infected with COVID-19.

The overall incidence of mortality in the present study was 31.18%, slightly higher than the local study by Tomacruz et al. of 25%,[21] and international studies with estimates ranging from 9-38%.[6–18] In a meta-analysis of 348 studies and over 300,000 CKD patients with COVID-19, the pooled mortality estimate was 28.11%.[3]

The authors identified several factors that increased the odds of mortality among ESRD patients. Increasing age was associated with death, which is similar to the results of previous studies.[11–13,15,18,22] Nonetheless, older age is a known factor affecting the survival of COVID-19 patients, not just the ESRD patients, given that older individuals tend to have more comorbidities and poorer immune status. [12]

The present study also shows that, sex is a risk factor for mortality which was not observed in previous studies among ESRD patients with COVID-19.[12,21,23] Meanwhile, one study focusing on hemodialysis patients with COVID-19 reported that the male sex was a significant predictor of mortality.[24] A similar trend was observed in the general population infected with COVID-19, wherein males were more likely to die than females.[25,26] Nonetheless, several studies concluded that, female patients with CKD are more likely to die than males, which could explain the current study findings.[27,28] According to De La Mata, et al., poorer survival among female CKD patients may be attributed to non-adherence to maintenance drugs, less access to health services, higher symptom burden and severity, and lower quality of life while on dialysis.[28] Moreover, females tend to have poorer outcomes after cardiovascular events which is quite common among patients with CKD.

DM and CAD were also found to increase the odds of mortality in the current study but, were not observed in other published studies.[10,12,16,21] In one meta-analysis comprised of hemodialysis patients, cardiovascular disease was significantly lower in survivors than non-survivors (OR=0.73); however, DM was not considered as a factor for mortality.[24] Patients with CAD may have a weaker cardiac function, thus, are more likely to experience acute cardiovascular events leading to a higher mortality risk. Although DM was not observed as a risk factor for ESRD patients, this comorbidity was considered the most important cause of mortality among hospitalized COVID-19 patients based on one meta-analysis.[29]

Although oxygen saturation on admission was not a significant predictor, the pulmonary function of hospitalized patients may worsen during admission. In this study, intubation shows increased mortality odds, similar to the previous results of the studies. In the local study by Tomacruz et al., 75% of patients who underwent mechanical ventilation died compared to 8% of those who underwent non-invasive ventilation and no ventilator support.[21]

Another significant predictor of mortality in this study was encephalopathy which was observed in only 6% of the patients. Although encephalopathy was not identified as a risk factor for mortality among ESRD patients, several studies have also noted this condition among COVID-19-infected individuals.[30] One study focused on dialysis patients reported that 10% of deaths were attributed to encephalopathy.[11] This can be explained by the fact that most encephalopathy patients with COVID-19 are older and have higher comorbidities.[30] COVID-19 patients with encephalopathy are also more likely to require critical care and intubation and have higher mortality rates.[30,31]

Although receipt of treatment modalities such as azithromycin, dexamethasone, and hemoperfusion showed

higher odds of mortality on the univariable analysis, these factors were no longer significant in the multivariable analysis. It was possible that patients with worse health status during the course of admission and those with comorbidities were given these treatment modalities; thus, when intubation and comorbidities were included in the analysis, these treatment modalities were no longer statistically significant.

The study has several limitations. First, the study only included hospitalized moderate-to-severe ESRD patients admitted at the NKTI. As these patients require hospitalization and given their current health status, a poorer prognosis is expected, as evidenced by the high mortality rate. Restriction to this population, however, minimizes confounding bias attributed to COVID-19 severity since mild cases tend to have better outcomes. The characteristics of patients admitted to NKTI may also differ from those hospitalized in other institutions (i.e., private hospitals). Thus, the generalizability of the results of this study is limited. Second, only routinely collected data are available from medical charts, which is a major limitation of this retrospective review. Moreover, other potential factors like BMI, electrolytes, maintenance medications, duration and frequency of RRT were not collected; thus, were not included in the analysis. Most patients have no data on inflammatory markers, which may also influence patient prognosis. Third, it has been known that the predominant COVID-19 variant had changed over time, and the differences in the COVID-19 variant could influence the present signs and symptoms, and patient outcomes in the study. However, the researcher cannot control its potential confounding effect due to the lack of data regarding the COVID-19 variant from the medical charts. Lastly, the vaccination status may influence the severity and outcomes of ESRD patients; however, this was not considered in the present study.

CONCLUSION

Patients with ESRD and COVID-19 showed a high in-hospital mortality rate. Older age, diabetes mellitus, coronary artery disease, encephalopathy, and intubation increased the odds of mortality. Meanwhile, males had lower odds of mortality than females.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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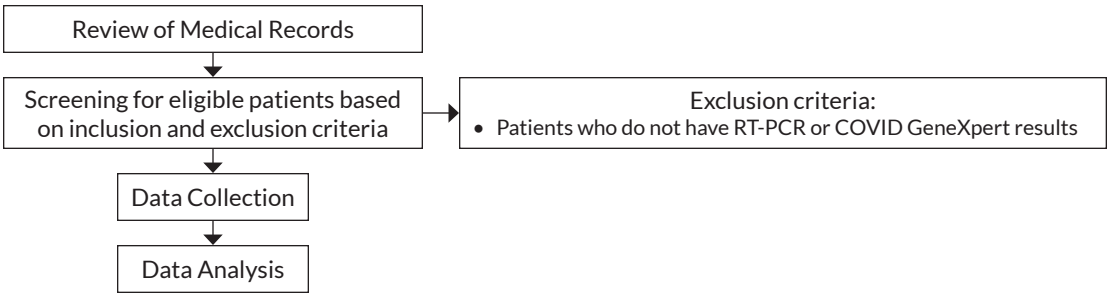
APPENDICES

Appendix A. Operational Definition of Variables

- Age (in years) on hospital admission
- Sex of patient based on medical charts. Categorized as male/female.
- Comorbidities refer to any of the following patient self-reported conditions on admission based on medical charts: hypertension, diabetes mellitus, coronary artery disease, heart failure, other cardiac disease, asthma, chronic obstructive pulmonary disease, OSA, PTB, stroke, seizure, encephalopathy, other neurologic disease, others.
- Vital sign – (first recorded value of patient on admission)
    - Heart rate categorized as normal (60-100 bpm) or low (<60 bpm) or high (>100 bpm)
    - Respiratory rate cateregorized as normal (12-20 cpm) or low (<12 cpm) or high (>20 cpm)
    - Oxygen saturation categorized as normal (95-100%) or abnormal (<95%)
    - Systolic blood pressure categorized as normal (110-130 mmHg) or low (<110 mmHg) or High (>130 mmHg)
    - Diastolic blood pressure categorized as normal (60-80 mmHg) or low (<60 mmhg) or high (>80 mmHg)
    - Highest temperature (in ℃) categorized as normal (<37.8 ℃) or fever (≥37.8 ℃)
- Management – Whether or not patient was given the following: azithromycin, tocilizumab, remdesivir, dexamethasone, hemoperfusion. Categorized as yes/no.
- RRT – patient underwent RRT during hospital stay. Categorized as yes/no.
- Intubation – patient underwent tracheal intubation during hospital stay. Categorized as yes/no.
- ICU admission – patient was admitted to the ICU during hospital stay. Categorized as yes/no.
- In-hospital mortality – patient died due to any cause during hospital stay. Categorized as yes/no.



Appendix B. Study flow diagram.

Appendix C. Screening of potential predictors of in-hospital mortality (n=449)

	Crude OR (95% CI)	*P* value
Age (in years)	1.03 (1.02-1.05)	**<0.0001***
Sex		
Female	Ref	Ref
Male	0.73 (0.49-1.09)	**0.128**
Comorbidities, % yes (Ref: Without)		
Hypertension	1.74 (1.06-2.88)	**0.029***
Diabetes mellitus	2.34 (1.56-3.52)	**<0.0001***
Coronary artery disease	2.18 (1.45-3.27)	**<0.0001***
Heart failure	0.89 (0.52-1.51)	0.662
Other cardiac disease	1.01 (0.48-2.13)	0.974
Asthma	0.48 (0.10-2.27)	0.356
COPD	2.61 (0.93-7.36)	**0.069**
OSA	0.73 (0.08-7.12)	0.789
PTB	1.48 (0.79-2.78)	0.221
Stroke	2.37 (1.31-4.27)	**0.004***
Seizure	1.57 (0.59-4.22)	0.368
Encephalopathy	4.30 (1.85-9.99)	**0.001***
Other neurologic disease	0.73 (0.08-7.12)	0.789
Other disease	1.10 (0.10-12.28)	0.936
Vital signs on admission		
Heart rate		
Normal	Ref	Ref
Low	0.19 (0.01-3.41)	0.258
High	0.80 (0.49-1.30)	0.364
Respiratory rate		
Normal	Ref	Ref
High	1.35 (0.90-2.04)	**0.151**
Oxygen saturation		
Normal	Ref	Ref
Abnormal	1.36 (0.87-2.13)	**0.176**
Systolic blood pressure		
Normal	Ref	Ref
Low	1.53 (0.76-3.05)	0.230
High	0.72 (0.47-1.10)	**0.123**
Diastolic blood pressure		
Normal	Ref	Ref
Low	2.96 (1.32-6.64)	**0.009***
High	0.60 (0.38-0.95)	**0.030***
Highest temperature		
Normal	Ref	Ref
Fever	1.21 (0.78-1.88)	0.405
Management (Treatment received), (Ref: No)		
Azithromycin	1.84 (1.20-2.83)	**0.006***
Tocilizumab	2.08 (0.86-5.03)	**0.102**
Remdesivir	3.00 (0.66-13.59)	**0.154**
Dexamethasone	1.88 (1.20-2.93)	**0.006***
Hemoperfusion	1.87 (1.03-3.40)	**0.040***
RRT		
HD only	Ref	Ref
PD only	0.19 (0.08-0.46)	**<0.0001***
HD and PD	0.68 (0.31-1.52)	0.350
Intubation		
No	Ref	Ref
Yes	25.53 (13.37-48.75)	**<0.0001***
ICU admission		
No	Ref	Ref
Yes	8.40 (3.03-23.28)	**<0.0001***