

ORIGINAL ARTICLE

Risk factors for the mortality of hemodialysis patients with COVID-19: A multicenter study from the overall hemodialysis population in Wuhan

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Funding information

This work was financially supported by the National Natural Science Foundation of China (81700603, 81961138007, 81974096, 81770711, 81522010), the National Key Research and Development Program (2020YFC0845800, 2020YFC0844700, 2018YFC1314000), and the Program for HUST Academic Frontier Youth Team (2017QYTD20).

Abstract

Introduction: Maintenance hemodialysis (MHD) patients are highly threatened in the novel coronavirus disease 2019 (COVID-19) pandemic, but evidence of risk factors for mortality in this population is still lacking.

Methods: We followed outcomes of the overall MHD population of Wuhan, including 7154 MHD patients from 65 hemodialysis centers, from January 1 to May 4, 2020. Among them, 130 were diagnosed with COVID-19. The demographic and clinical data of them were collected and compared between survivors and nonsurvivors.

Results: Compared to the corresponding period of last year, the all-cause mortality rate of the Wuhan MHD population significantly rose in February, and dropped down in March 2020. Of the 130 COVID-19 cases, 51 (39.2%) were deceased. Advanced age, decreased oxygen saturation, low diastolic blood pressure (DBP) on admission, and complications including acute cardiac injury (HR 5.03 [95% CI 2.21–11.14], $p < 0.001$), cerebrovascular event (HR 2.80 [95% CI 1.14–6.86], $p = 0.025$) and acute respiratory distress syndrome (HR 3.50 [95% CI 1.63–7.51], $p = 0.001$) were identified as independent risk factors for the death of COVID-19. The median virus shedding period of survivors was 25 days, longer than the general population.

Conclusions: Maintenance hemodialysis patients are a highly vulnerable population at increased risk of mortality and prolonged virus shedding period in the ongoing COVID-19 pandemic. Advanced age, decreased oxygen saturation, low DBP on admission, and complications like acute cardiac injury are parameters independently associated with poor prognosis.

1 | INTRODUCTION

The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection widely encompassing asymptomatic infection, mild upper respiratory tract illness, severe viral pneumonia with respiratory failure and even death,¹⁻³ but the underlying risk factors and mechanisms associate with these differences in clinical course are not well understood. In Wuhan, the initial “storm eye” of the novel coronavirus disease 2019 (COVID-19) pandemic, no more newly confirmed cases were identified after a universal screening of nucleic acid testing (NAT) in the overall population,⁴ giving great opportunity for retrospectively depicting the full spectrum of infection.

Patients with end-stage kidney disease (ESKD) are highly vulnerable populations during the COVID-19 pandemic. Because of their advanced age, uremic state, high comorbidity burden, and poor nutrition,⁵ ESKD patients are at increased risk of opportunistic infections, developing severe complications, admission to intensive care unit (ICU), or even death. In addition, underlying chronic kidney disease itself has been identified as an independent risk factor for mortality. A previous study demonstrated that elevated baseline serum creatinine level was associated with a hazard ratio for death of 2.10.⁶

Goicoechea et al.⁷ analyzed clinical course and outcomes of 36 MHD patients with COVID-19 from a single center in Spain, in which they found high infection rate and poor prognosis of COVID-19 in MHD patients. Valeri et al. reported 59 cases of COVID-19 in patients with ESKD on dialysis from a single medical center in New York, 18 of them died.⁸ These researchers provided very useful information on the prognosis of MHD patients with COVID-19. However, these studies were also inevitably limited by their small sample sizes and data source from single centers. In this regard, large and multicenter studies are urgently needed to comprehensively describe the outcomes and related risk factors of MHD patients with COVID-19. Our earlier study in which we analyzed data of 7154 maintenance hemodialysis (MHD) patients from 65 medical institutions in Wuhan, found high prevalence and poor short-term outcomes of COVID-19 in this population.⁹ However, many patients were still hospitalized by the cut-off date of the study, so outcomes were not clear at that time.

Here, using data collected from a registration system that included all patients undergoing hemodialysis in Wuhan, we aim to describe the clinical outcomes and viral shedding of MHD patients with COVID-19, and to explore risk factors for mortality.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This multicenter, observational study included 7154 MHD patients from 65 hemodialysis centers of Wuhan Hemodialysis Quality Control Center (WHQCC). From January 1 to March 10, 2020, through strict entrance screening of body temperature and respiratory or digestive tract symptoms, and universal monitoring of chest CT and blood C-reactive protein (CRP) and complete blood count in all the MHD

patients, 154 patients with NAT-confirmed COVID-19 were identified out of 7154 MHD patients throughout Wuhan.⁹ After excluding 23 patients without verbal consent and one patient who lost contact, a total number of 130 cases were finally included in the study. COVID-19 was diagnosed according to the New Coronavirus Pneumonia Prevention and Control Program (7th edition) published by the National Health Commission of China.⁹ The study was approved by the Ethics Committees of all participating institutions.

2.2 | Data collection

Data of the 130 MHD patients with COVID-19 were followed and collected through the online registration system of WHQCC. A standardized data collection form was used to collect demographic, epidemiological, clinical, laboratory, treatment and outcome data, and filled by the liaison men or women of the units under the WHQCC. All data were cross-checked by two physicians (HT and CT). Direct communication with patients or their families or attending doctors proceeded if important data were missing from the records or clarification was needed. The clinical outcomes were followed till May 4, 2020.

2.3 | Definitions

The degree of severity of COVID-19 (mild vs. moderate vs. severe vs. critical) was defined according to the New Coronavirus Pneumonia Prevention and Control Program (7th edition).⁹ Fever was defined as a temperature of at least 37.3°C. Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin definition. It is defined as an acute onset of hypoxia and bilateral pulmonary opacities not fully explained by a cardiac cause. Acute onset is specified to be within 1 week of a precipitating illness and hypoxia is determined by a PaO_2 to FiO_2 ratio ≤ 300 mm Hg while receiving a minimum of 5-cm H_2O of PEEP.¹⁰ Acute cardiac injury was diagnosed if the serum levels of cardiac biomarkers (e.g., troponin I) were above the 99th percentile upper reference limit or new abnormalities were shown in electrocardiography and echocardiography. Acute hepatic injury was defined as an elevation in aspartate aminotransferase or alanine aminotransferase of >10 times the upper limit of normal.^{11,12} These complications were diagnosed and confirmed that presented during the clinical course of COVID-19 by two physicians (HT and CT). The date of disease onset was defined as the day when the symptoms were noticed. The virus shedding period was calculated from the date of first positive NAT to the date of two consecutive negative NAT.

2.4 | Statistical analysis

Continuous variables were presented as median and interquartile range (IQR) or mean and standard deviation (SD). Categorical variables were expressed as number (%). For continuous variables, Student's *t* test was used for normal distributed data, and Mann-Whitney *U* nonparameter test was used for nonnormal distributed data. The Pearson's χ^2 test,

Fisher's exact test, and the χ^2 test with Yates' correction were applied for categorical variables. Time to clinical outcomes was defined as the time from disease onset to events. The univariable and multivariable cox regression models adjusted for age, sex, and comorbidities (cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease and tumor) were used to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between individual factors and death risk in MHD patients with COVID-19.

3 | RESULTS

3.1 | All-cause mortality rates of MHD patients in Wuhan during COVID-19 pandemic compared to the corresponding period of last year

The data of all-cause mortality rates of MHD patients were obtained from WHQCC. A total of 191 deaths were recorded from January 1, 2020, to April 30, 2020, in Wuhan city. As shown in Figure 1, the all-cause mortality rate in January 2020 was 0.70 deaths per 100 populations, lower than the corresponding period of last year, showing an improving surviving rate of the Wuhan hemodialysis population along with time. However, the all-cause mortality rate in February 2020 suddenly rose to 1.6 deaths per 100 population, much higher than 0.77 deaths per 100 population in last year. After that, the mortality rate dropped down to 0.60 deaths per 100 population in March 2020 and 0.25 deaths per 100 population in April 2020, which were lower than rates in the corresponding period of last year.

3.2 | Comparison of baseline characteristics between survivors and nonsurvivors

By the date of May 4, 2020, of the 130 MHD patients with COVID-19, 79 patients (60.8%) were fully recovered and discharged from hospital, 51 patients (39.2%) were deceased (Table 1).

The mean age of nonsurvivors (65.61 ± 12.91 years) was higher than that of the survivors (61.58 ± 13.13 years), but no significant difference was identified between the two groups. There were also no significant differences observed between survivors and nonsurvivors in sex, body mass index, smoking status, and close contact history with COVID-19 patients. It seemed that there were more household clustering infections in nonsurvivors than survivors (29.41% vs. 22.78%).

The primary cause of ESKD was dominated by diabetic nephropathy in survivors, but by hypertensive kidney disease in nonsurvivors. Glomerulonephritis was more common in nonsurvivors than survivors (26% vs. 11.39%, $p = 0.032$). Other causes including renal allograft dysfunction, obstructive nephropathy, urate nephropathy, kidney cancer, drug-related kidney injury, and kidney disease of unknown reason. About 70% of the patients in either survivors or nonsurvivors were accompanied by cardiovascular disease, but no significant differences in comorbidities were identified between the two groups.

Medication history of renin-angiotensin-aldosterone system inhibitors were more common in nonsurvivors than in survivors. No significant differences in previous hemodialysis modality, hemodialysis access, hemodialysis frequency or time on dialysis were found between survivors and nonsurvivors.

3.3 | Comparison of clinical characteristics, laboratory, and radiologic findings between survivors and nonsurvivors

Clinical characteristics of the patients and laboratory and radiologic findings at the time of diagnosis are presented in Table 2. Almost all types of symptoms including fever, fatigue, cough and diarrhea were more common in nonsurvivors when compared with survivors, especially for sputum production (37.25% vs. 18.99%, $p = 0.021$) and dyspnea (39.22% vs. 16.46%, $p = 0.004$). Accordingly, nonsurvivors had lower levels of blood oxygen saturation on admission than

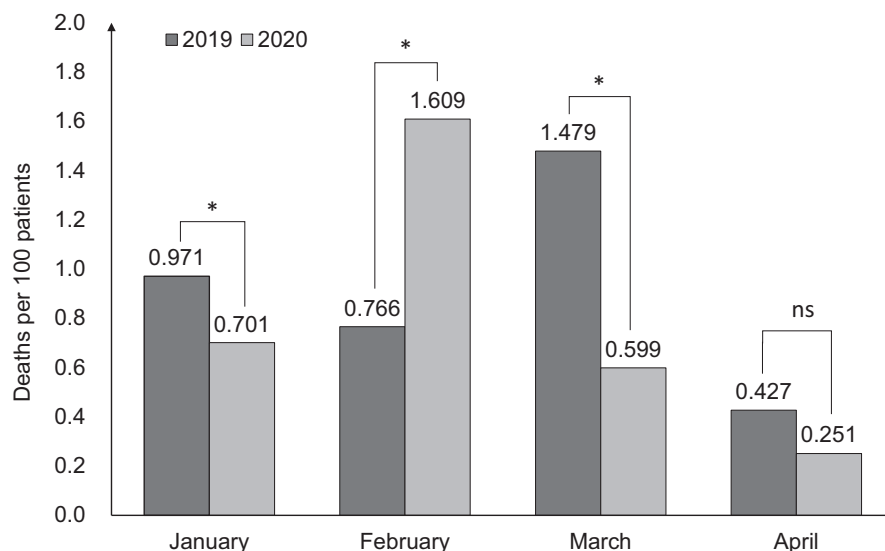


FIGURE 1 All-cause mortality rates of MHD patients in Wuhan during the COVID-19 pandemic and the corresponding period of 2019. p values were calculated by Fisher's exact test. * $p < 0.05$

TABLE 1 Baseline characteristics of MHD patients

Characteristics	Survivors	Nonsurvivors	p value
	(N = 79)	(N = 51)	
Age (mean [SD], year)	62 ± 13	66 ± 13	0.09 ^a
Sex (n, %)			
Male	44 (56%)	31 (61%)	0.6 ^f
Female	35 (44%)	20 (39%)	
BMI (mean ± SD, kg/m ²)	21.8 (20.0–25.1)	21.2 (16.5–25.4)	0.2 ^b
Current smoker (n, %)	24 (30%)	14 (28%)	0.8 ^f
Contact history with COVID-19 patients (n, %)	40 (51%)	21 (43%)	0.4 ^f
COVID-19 patients in the family (n, %)	18 (23%)	15 (29%)	0.4 ^f
Primary causes of ESKD (n, %)			
Diabetic nephropathy	25 (32%)	10 (20%)	0.1 ^f
Hypertensive kidney disease	22 (28%)	19 (38%)	0.2 ^f
Glomerulonephritis	9 (11%)	13 (26%)	0.03 ^{*,f}
Polycystic kidney disease	3 (4%)	1 (2%)	0.9 ^d
Lupus nephritis	1 (1%)	3 (6%)	0.3 ^d
Others	24 (30%)	4 (8%)	0.003 ^{*,f}
Coexisting disorders (n, %)			
Cardiovascular disease	55 (70%)	33 (70%)	0.9 ^f
Diabetes mellitus	30 (38%)	14 (30%)	0.3 ^f
Chronic obstructive pulmonary disease	3 (4%)	2 (4%)	1.000 ^d
Cancer	0 (0%)	2 (4%)	0.1 ^e
Hepatitis B virus infection	6 (8%)	4 (9%)	1.000 ^d
Hepatitis C virus infection	3 (4%)	0 (0%)	0.5 ^d
Previous medication (n, %)			
ACEI/ARB	23 (29%)	22 (49%)	0.03 ^{*,f}
Immunosuppressant	5 (6%)	2 (4%)	0.9 ^d
Previous hemodialysis modality (n, %)			
Hemodialysis	73 (92%)	49 (98%)	0.3 ^d
Hemodiafiltration	24 (30%)	13 (26%)	0.6 ^f
Hemoperfusion	2 (3%)	1 (2%)	0.9 ^d
Hemodialysis access (n, %)			
AVF	49 (63%)	32 (63%)	0.3 ^f
CVC	28 (35%)	17 (33%)	0.2 ^f
CVC/AVF	1 (1%)	1 (2%)	0.5 ^e
AVG	1 (1%)	1 (2%)	0.9 ^e

(Continues)

TABLE 1 (Continued)

Characteristics	Survivors	Nonsurvivors	p value
	(N = 79)	(N = 51)	
Hemodialysis frequency (times/week, n, %)			
<3	26 (33%)	10 (20%)	0.1 ^f
=3	53 (67%)	41 (80%)	
Hemodialysis months (median, IQR)	31 (10–72)	34 (9–63)	0.7 ^b

Note: Continuous variables were presented as median and interquartile range (IQR) or mean and standard deviation (SD). *p* values were calculated by Student's *t* test for normal distributed data (a) or Mann-Whitney *U* nonparameter test for skewed distributed data (b). Categorical variables were expressed as number (%). *p* values were calculated by χ^2 test with Yates' correction (d), Fisher's exact test (e) or Pearson's χ^2 test (f).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; CVC, central venous catheter; ESKD, end stage kidney disease.

survivors. In addition, there were more asymptomatic patients in survivors than in nonsurvivors (39.24% vs. 15.69%, *p* = 0.004). The mean systolic blood pressure (SBP) showed no difference between the two groups, but diastolic blood pressure (DBP) was significant lower in nonsurvivors.

Of all pulmonary CT scans performed on admission, the majority of the radiological abnormalities revealed were ground-glass or patchy opacity in both groups, but consolidation was more often in nonsurvivors, although no significant differences were found between the two groups. Also, no significant differences in lesion region were observed.

Data from laboratory tests on admission showed that compared with survivors, nonsurvivors had lower platelet count, lymphocyte count, and higher CRP level. The median level of serum intact parathyroid hormone (i-PTH) was lower in nonsurvivors than in survivors (115.05 [IQR 22.70–273.70] pg/ml vs. 291.90 [IQR 228.30–530.50] pg/ml, *p* = 0.028).

Complications including acute cardiac injury, acute hepatic injury, cerebrovascular event and ARDS were commonly seen in these patients, especially in nonsurvivors. More than half of the nonsurvivors had acute cardiac injury, 28.21% had acute hepatic injury, 27.91% had ARDS and 21.21% had cerebrovascular event, all were significant higher than that in survivors.

3.4 | Comparison of treatments, outcomes, and virus shedding period between survivors and nonsurvivors

As shown in Table 3, compared to survivors, nonsurvivors had shorter time interval between the date of last dialysis received before COVID-19 diagnosis to the date of dialysis restart (2.0 [IQR 1.0–4.0] days vs. 4.0 [IQR 3.0–6.5] days, *p* < 0.001). More patients

TABLE 2 Clinical characteristics, laboratory and radiologic findings of MHD patients with COVID-19

Characteristics	Survivors		Nonsurvivors		p value
	(N = 79)		(N = 51)		
Symptoms (n, %)					
Fever	37 (47%)		31 (61%)		0.1 ^f
Fatigue	30 (38%)		27 (53%)		0.1 ^f
Sore throat	4 (5%)		7 (14%)		0.2 ^d
Cough	23 (29%)		23 (45%)		0.06 ^f
Sputum production	15 (19%)		19 (37%)		0.02 ^{*,f}
Nausea/Vomiting	11 (14%)		7 (14%)		0.9 ^f
Diarrhea	9 (11%)		8 (16%)		0.5 ^f
Dyspnea	13 (16%)		20 (39%)		0.004 ^{*,f}
Asymptomatic	31 (39%)		8 (16%)		0.004 ^{*,f}
Basal oxygen saturation	95 (93–100)		90 (80–95)		<0.001 ^{*,b}
Systolic blood pressure	148 (135–160)		150 (136–160)		0.8 ^b
Diastolic blood pressure	90 (77–90)		80 (70–82)		0.005 ^{*,b}
Radiologic findings					
CT image features (n, %)		N = 68		N = 48	
Ground-glass/patchy opacity	56 (82%)		40 (83%)		0.9 ^f
Consolidation	1 (1%)		4 (8%)		0.2 ^d
Fibrosis	7 (10%)		2 (4%)		0.4 ^d
Others	4 (6%)		2 (4%)		0.9 ^d
Lesion region (n, %)		N = 67		N = 46	
Bilateral lung	57 (85%)		41 (89%)		0.5 ^f
Left lung	4 (6%)		3 (7%)		0.9 ^d
Right lung	6 (9%)		2 (4%)		0.6 ^d
Laboratory findings					
Hemoglobin (10 ⁹ /L)	104.67 ± 17.56		101.15 ± 22.26		0.4 ^a
Platelets (10 ⁹ /L)	147.0 (115.5–204.5)		122.00 (87.5–175.0)		0.05 ^b
White blood cells (10 ⁹ /L)	4.69 (3.70–7.27)		5.36 (4.04–7.23)		0.7 ^b
Neutrophils (10 ⁹ /L)	3.83 (2.70–5.52)		4.39 (3.08–6.49)		0.6 ^b
Lymphocytes (10 ⁹ /L)	0.81 (0.52–1.08)		0.57 (0.32–1.15)		0.09 ^b
Eosnophils (10 ⁹ /L)	0.03 (0.01–0.07)		0.01 (0–0.07)		0.1 ^b
Serum albumin (mg/L)	37.10 (34.65–40.75)		38.20 (33.50–40.80)		0.9 ^b
ALT (U/L)	12.00 (9.00–17.00)		10.00 (6.75–18.25)		0.2 ^b
AST (U/L)	15.40 (11.50–23.75)		15.00 (10.53–25.25)		0.9 ^b
Total bilirubin (μmol/L)	7.70 (5.30–10.00)		7.05 (5.25–9.33)		0.7 ^b
Creatine kinase (IU/L)	72.00 (38.00–150.50)		92.90 (40.50–201.00)		0.4 ^b
Creatine kinase-MB (IU/L)	13.15 (8.00–24.18)		13.80 (9.48–36.30)		0.5 ^b
Lactate dehydrogenase (U/L)	249.00 (162.88–328.88)		334.00 (179.25–628.00)		0.2 ^b
Serum calcium (mmol/L)	2.15 ± 0.30		2.14 ± 0.25		0.9 ^a
Serum phosphorous (mmol/L)	1.81 (1.52–2.22)		1.77 (1.26–2.70)		0.8 ^b
i-PTH (pg/ml)	291.90 (228.30–530.50)		115.05 (22.70–273.70)		0.03 ^{*,b}
Serum D-dimer (mg/L)	1.25 (0.66–5.84)		2.38 (0.85–5.14)		0.6 ^b
CRP (mg/L)	14.63 (8.33–44.95)		41.76 (20.36–117.45)		0.07 ^b
Complications (n, %)					
Acute cardiac injury	N = 65	7 (13%)	N = 39	18 (55%)	<0.001 ^{*,f}

(Continues)

TABLE 2 (Continued)

Characteristics	Survivors		Nonsurvivors		p value
	(N = 79)		(N = 51)		
Acute hepatic injury	N = 53	6 (9%)	N = 33	11 (28%)	0.01 ^{*,f}
Cerebrovascular event	N = 62	3 (5%)	N = 33	7 (21%)	0.03 ^{*,d}
ARDS	N = 73	4 (5%)	N = 43	12 (28%)	0.001 ^{*,f}
Disease severity					
Mild/Moderate	67 (85%)		36 (71%)		0.05 ^f
Severe/Critical	12 (15%)		15 (29%)		

Note: Continuous variables were presented as median and interquartile range (IQR) or mean and standard deviation (SD). *p* values were calculated by Student's *t* test for normal distributed data (a) or Mann-Whitney *U* nonparameter test for skewed distributed data (b). Categorical variables were expressed as number (%). *p* values were calculated by χ^2 test with Yates' correction (d), Fisher's exact test (e), or Pearson's χ^2 test (f).

Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CRP, C-reactive protein; i-PTH, intact parathyroid hormone.

in nonsurvivors switch to receive CRRT from normal hemodialysis (57.50% vs. 17.81%, $p < 0.001$). No significant differences in dialysis frequency or changes of dialysis frequency were observed between survivors and nonsurvivors.

Most of the patients in both groups received antivirals and antibiotics, but prescription of corticosteroid was more common in nonsurvivors (29.73% vs. 11.27%, $p = 0.017$), while prescription of traditional Chinese medicine was more common in survivors (82.46% vs. 59.38%, $p = 0.017$).

By the end of follow-up, nonsurvivors died a median time of 18 days after symptom onset. The median virus shedding period of survivors was 25 days, but for nonsurvivors, only two patients' NATs turned negative before deceased.

3.5 | Risk factors for mortality of COVID-19 in hemodialysis patients

No significant association of established risk factors in general population like sex and comorbidities (cardiovascular disease, diabetes mellitus, COPD and tumor) were found in MHD patients (Table 4) except age (HR 1.03 [95% CI 1.00–1.05], $p = 0.035$). After adjusting for age, sex and comorbidities in multivariable analyses, we found that decreased oxygen saturation (HR 0.91 [95% CI 0.86–0.96], $p < 0.001$) and low DBP (HR 0.971 [95% CI 0.94–1.00], $p = 0.041$) on admission was significantly associated with higher mortality. Increased creatine kinase (CK) and lactate dehydrogenase (LDH) levels on admission were also associated with worse outcome, while elevated CRP (HR 1.007 [95% CI 1.000–1.014], $p = 0.06$) did not reach the level of statistical significance. Patients with complications including acute cardiac injury, cerebrovascular event and ARDS were at significant higher risk of death, and the risk was highest for those with acute cardiac injury (HR 5.03 [95% CI 2.21–11.14], $p < 0.001$). Prescription of glucocorticoid was also associated with higher risk of death (HR 2.40 [95% CI 1.13–5.10], $p = 0.023$). Other treatments including prescription of drugs and mechanical ventilation were not significantly associated

with mortality, except for traditional Chinese medicine which reduced the risk of death in the univariate analysis (HR 0.437 [95% CI 0.208–0.920], $p = 0.029$), but it was less pronounced when adjusted by age, sex, and comorbidities.

4 | DISCUSSION

Here, we presented clinical characteristics, treatments and outcomes of 130 cases of NAT confirmed COVID-19 in 7154 MHD patients from 65 hemodialysis centers in Wuhan. According to our findings, in the initial epicenter of the outbreak, Wuhan, MHD patients infected with SARS-CoV-2 have an increased risk of death than the general population. In particular, advanced age, low oxygen saturation and DBP on admission, as well as multiply complications, especially acute cardiac injury were identified as independent risk factors for death. However, previously reported risk factors for the general population, such as male sex, diabetes, lymphopenia, and D-dimer were not significantly associated. Patients died a median time of 18 days after symptom onset and the median virus shedding period of survivors was 25 days.

The mortality rate of MHD patients with COVID-19 was 39.2% in our study cohort, which was much higher than the general population in the same city (8%).¹³ In other case series of MHD patients with COVID-19, the mortality rates reported were varied by countries and areas. From a single center cohort in China, 16.2% MHD patients with COVID-19 died.¹⁴ Mortality rates reported in two case series from Italy were 41% in city Piacenza¹⁵ and 25% in city Brescia.¹⁶ In an observational single-center study in Spain, 30.5% MHD patients died,⁷ and a mortality rate of 31% was observed in ESKD patients either on hemodialysis or peritoneal dialysis from a single center in New York.⁸ The origins of patients were more diverse in our study which included patients from district hospitals and small centers, and the follow-up period was longer, which might both contributed to the high mortality rate.

It is a worldwide consensus that patients on hemodialysis have higher mortality risks compared with the general population.^{17,18} Therefore, it is of interest to clarify the influence of COVID-19

TABLE 3 Treatments and outcomes of MHD patients

Characteristics	Survivors		Nonsurvivors		p value
	(N = 79)		(N = 51)		
Time interval of dialysis restart after COVID-19 diagnosis (median, IQR, day)	N = 69	4.0 (3.0–6.5)	N = 31	2.0 (1.0–4.0)	<0.001 ^b
Present hemodialysis Modality (n, %)	N = 73		N = 40		
Hemodialysis		61 (84%)		16 (40%)	<0.001 ^f
CRRT		13 (18%)		23 (58%)	<0.001 ^f
Hemodiafiltration		4 (5%)		2 (5%)	1.000 ^d
Present hemodialysis frequency (times/week, n, %)	N = 74		N = 37		0.1 ^f
<3		43 (58%)		16 (43%)	
=3		31 (42%)		21 (57%)	
Changes of dialysis frequency before and after the epidemic n (%)	N = 74		N = 37		0.9 ^f
Decreased		28 (38%)		14 (38%)	
Unchanged		40 (54%)		19 (51%)	
Increased		6 (8%)		4 (11%)	
Drugs					
Antivirals	N = 71	54 (76%)	N = 43	38 (88%)	0.1 ^f
Antibiotics	N = 65	53 (82%)	N = 43	39 (91%)	0.2 ^f
Glucocorticoids	N = 71	8 (11%)	N = 37	11 (30%)	0.02 ^f
Chinese medicine	N = 57	47 (83%)	N = 32	19 (59%)	0.02 ^f
HFNC oxygen therapy or Noninvasive mechanical ventilation	N = 70	14 (20%)	N = 39	8 (21%)	0.9 ^f
Invasive mechanical ventilation	N = 69	1 (1%)	N = 39	2 (5%)	0.6 ^d
Hospitalized	N = 77	76 (99%)	N = 50	40 (80%)	0.001 ^d
Virus shedding period (day)	N = 79	25.0 (14.0–36.0)	N = 2	18.5 (8.3–19.5)	0.4 ^b
Days between onset and death or discharge	N = 76	43.0 (32.3–50.0)	N = 48	18.0 (9.3–27.8)	<0.001 ^b

Note: Continuous variables were presented as median and interquartile range (IQR) or mean and standard deviation (SD). *p* values were calculated by Student's *t* test for normal distributed data (a) or Mann-Whitney *U* nonparameter test for skewed distributed data (b). Categorical variables were expressed as number (%). *p* values were calculated by χ^2 test with Yates' correction (d), Fisher's exact test (e) or Pearson's χ^2 test (f).

Abbreviations: CRRT, continuous renal replacement therapy; HFNC, high flow nasal cannula.

pandemic on the death rate of the overall hemodialysis population. When we compared the all-cause mortality rate of the study cohort to that of the corresponding period of last year, a sudden and marked increase in mortality rate was found in February, 2020, more than doubled that of the same month last year. Interestingly, in March, 2020, the mortality rate dropped down to almost the same level as January 2020, but lower than the corresponding period of last year. According to the weekly average incidence rate of COVID-19 in the MHD population reported in our earlier study,⁹ the cases of COVID-19 in MHD patients began to rise on January 23, 2020, and peaked at January 30, 2020. After February 26, 2020, there were only sporadic cases diagnosed. Therefore, the sudden rise of mortality rate may be largely attributed to the COVID-19 cases diagnosed in the early phase of outbreak, and the patients who died of COVID-19 in February probably had a high chance of dying in the following months. The consumption of medical resources by COVID-19 is also an important factor affecting mortality. In April 2020, when the COVID-19 outbreak had been completely brought under control

in Wuhan, the mortality rate dropped down to almost the same as in the corresponding period of last year. These data showed that the impact of the epidemic on hemodialysis population has basically disappeared in April 2020.

In our study, male gender and underlying disease like diabetes was not significantly associated with high risk of death, which was inconsistency with previous studies of general population.^{19,20} However, glomerulonephritis as the primary cause of ESKD seemed to be associated with increased mortality. Lupus nephritis was also more common in nonsurvivors. Liu et al.²¹ reported that IgA nephropathy is the major cause of primary glomerulonephritis in China. Patients with primary or secondary glomerular diseases often have a drug history of immunosuppressive medications, and underlying immune dysfunction. The delicate balance between protective and dysregulated host immune responses is key in determining the course and outcome COVID-19. Nonetheless, there are limited data regarding the outcomes of COVID-19 in adult patients with underlying glomerular diseases. A recent study using

TABLE 4 Risk factors associated with mortality of MHD patients with COVID-19

Characteristics	Univariable HR	p value	Adjusted HR	p value ^a
Male sex (n, %) ^b	1.22 (0.64–2.31)	0.5	1.46 (0.76–2.82)	0.3
Age (mean [SD], year) ^c	1.03 (1.00–1.05)	0.02	1.03 (1.00–1.05)	0.04
Coexisting disorders				
Cardiovascular disease ^d	0.90 (0.46–1.76)	0.8	0.91 (0.47–1.75)	0.8
Diabetes mellitus ^e	0.61 (0.27–1.39)	0.2	0.61 (0.31–1.20)	0.1
Chronic obstructive pulmonary disease ^f	1.50 (0.36–6.28)	0.6	0.79 (0.11–5.97)	0.8
Cancer ^g	2.72 (0.65–11.34)	0.2	1.70 (0.34–8.36)	0.5
Current smoker (n, %)	0.87 (0.43–1.79)	0.7	0.71 (0.34–1.50)	0.4
Primary causes of ESKD				
Diabetic nephropathy	0.86 (0.42–1.78)	0.7	0.33 (0.09–1.20)	0.1
Hypertensive kidney disease	1.57 (0.83–2.96)	0.2	1.55 (0.82–2.96)	0.2
Glomerulonephritis	1.68 (0.77–3.67)	0.2	2.07 (1.00–4.29)	0.05
Polycystic kidney disease	0.53 (0.07–3.88)	0.5	0.61 (0.08–4.78)	0.6
Lupus nephritis	0.94 (0.13–6.96)	0.9	2.45 (0.30–20.21)	0.4
Changes in dialysis frequency before and after the epidemic n (%)				
Unchanged	1.00 (Reference)		1.00 (Reference)	
Decreased	1.23 (0.58–2.61)	0.6	0.74 (0.34–1.58)	0.4
Increased	1.15 (0.33–4.01)	0.8	1.79 (0.46–6.97)	0.4
Dialysis months	1.00 (0.99–1.01)	0.8	1.00 (0.99–1.01)	0.8
Basal oxygen saturation	0.92 (0.88–0.96)	<0.001	0.91 (0.86–0.96)	<0.001
Systolic blood pressure	1.00 (0.98–1.02)	0.8	1.01 (0.99–1.02)	0.4
Diastolic blood pressure	0.96 (0.93–0.99)	0.004	0.97 (0.94–1.00)	0.04
Laboratory findings				
White blood cells (10 ⁹ /L)	1.02 (0.91–1.13)	0.8	1.07 (0.94–1.21)	0.3
Lymphocytes (10 ⁹ /L)	1.00 (0.99–1.02)	0.8	1.00 (0.99–1.02)	0.6
Serum albumin (mg/L)	1.00 (0.96–1.04)	0.8	0.99 (0.95–1.04)	0.7
Creatine kinase (IU/L)	1.000 (1.000–1.000)	0.05	1.000 (1.000–1.000)	0.04
lactate dehydrogenase (U/L)	1.000 (1.000–1.001)	0.02	1.001 (1.000–1.001)	0.04
i-PTH (pg/ml)	1.00 (1.00–1.00)	0.5	1.00 (1.00–1.00)	0.8
Serum D-dimer (mg/L)	1.00 (1.00–1.00)	0.5	1.00 (1.00–1.00)	0.6
CRP (mg/L)	1.01 (1.00–1.01)	0.06	1.00 (1.00–1.01)	0.3
Complications				
Acute hepatic injury	2.35 (1.05–5.28)	0.04	2.43 (0.99–6.00)	0.05
Acute cardiac injury	3.79 (1.79–8.01)	<0.001	5.03 (2.21–11.44)	<0.001
ARDS	3.72 (1.85–7.48)	<0.001	3.50 (1.63–7.51)	0.001
Cerebrovascular event	2.61 (1.05–6.44)	0.04	2.80 (1.14–6.86)	0.03
Disease severity	2.20 (1.14–4.23)	0.02	1.90 (0.97–3.71)	0.06
Drugs				
Antivirals	1.35 (0.47–3.84)	0.6	2.38 (0.83–6.80)	0.1
Antibiotics	1.73 (0.53–5.66)	0.4	2.69 (0.88–8.18)	0.1
Glucocorticoids	1.99 (0.94–4.22)	0.07	2.40 (1.13–5.10)	0.02
Chinese medicine	0.44 (0.21–0.92)	0.03	0.54 (0.24–1.22)	0.1

Note: HRs (hazard ratio) and 95% CIs (confidence interval) were calculated by univariable and multivariable Cox regression models.

Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; ESKD, end stage kidney disease; i-PTH, intact parathyroid hormone.

^aAdjusted age, sex, comorbidities (cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease and cancer).

^bAdjusted age, comorbidities (cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease and cancer).

^cAdjusted sex, comorbidities (cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease and cancer).

^dAdjusted age, sex, diabetes mellitus, chronic obstructive pulmonary disease and cancer.

^eAdjusted age, sex, cardiovascular disease, chronic obstructive pulmonary disease and cancer.

^fAdjusted age, sex, cardiovascular disease, diabetes mellitus and cancer.

^gAdjusted age, sex, cardiovascular disease, diabetes mellitus and chronic obstructive pulmonary disease.

an International Registry of COVID infection in glomerulonephritis (IRoc-GN) found that patients with glomerulonephritis had significantly higher mortality (15% vs. 5%, respectively) and acute kidney injury (39% vs. 14%) than COVID-19 cases from the general population without glomerulonephritis. But receiving immunosuppression at presentation did not increase the risk of death or acute kidney injury in the glomerulonephritis cohort.²² Thus, the specific mechanism implicated in the association between glomerulonephritis and increased mortality still needs further exploration. In laboratory findings, significant increased initial white blood cell count and CRP in patients who died compared with those still living were observed in previous study on MHD patients with COVID-19.⁸ Another study of MHD patients with COVID-19 found that increased LDH levels and lower lymphocyte count one week after clinical onset were also associated with poor prognosis.⁷ We also identified elevated LDH level as a risk factor for mortality of MHD patients, which was shown to have prognostic value in *Pneumocystis jirovecii* pneumonia.²³ Lymphocyte counts and CRP levels were also associated but did not reach statistical significance. It is possible that the impaired immune status of these populations weakens the immune response to the infection. Although D-dimer greater than 1 µg/L was reported as a good predictive factor for identifying patients with poor prognosis at the early stage,¹⁹ D-dimer level on admission was not significantly different between nonsurvivors and survivors in our study. It should be noted that the timing of D-dimer measurement before or after dialysis affects the results, and high prevalence of elevated D-dimer was found in MHD patients without additional diseases (i.e., acute illness or predisposing chronic diseases).²⁴

We also found a shorter time interval of dialysis restart after COVID-19 diagnosis in nonsurvivors than survivors, which may be due to priority of hospital admission based on disease severity. So far, no specific drugs have been demonstrated effective for treating COVID-19. We found more patients using glucocorticoid in the nonsurvivor group and prescription of glucocorticoid was associated with increased mortality, which probably due to the fact that patients in these group had lower oxygen saturation and higher incidence of ARDS, and prescription of glucocorticoid were encouraged when patient has severe pulmonary damage according to the treatment protocols doctors referenced to. However, whether glucocorticoid is harmful or beneficial to COVID-19 remains to be confirmed.

In our cohort, the main parameters that independently predicted mortality were advanced age, lower oxygen saturation and DBP on admission, and multiply complications, especially acute cardiac injury. Lower oxygen saturation on admission usually indicated more severe pulmonary injury, which was consistent with the finding that most of the patients died of respiratory distress syndrome due to COVID-19 in our previous study and others.^{7,14,15} No significant difference was found in SBP on admission between survivors and nonsurvivors; thus, patients with lower DBP on admission may also have higher pulse pressure and worse arterial stiffness, which was demonstrated as an independent risk factor

for development of cardiovascular disease and incidence of cardiovascular events.^{25,26} Patients with complications like acute cardiac injury, acute hepatic injury, cerebrovascular event and ARDS were at significant higher risk of death, and acute cardiac injury was associated with a hazard ratio for death of 5.03. This finding is consistent with a previous study in the general population that patients with cardiac injury were at a higher risk of death with a hazard ratio of 4.26.²⁰ The usage of Chinese traditional drugs was found to be associated with a benign prognosis before adjusted by multiply parameters, but the specific kind of drugs patients taken was unclear and large randomized controlled trials were needed to clarify this association.

In the general hemodialysis population, the major risk factors associated with all-cause death include age, sex, initial dialysis status, primary disease (including diabetic nephropathy and hypertensive nephropathy), malnutrition, and vascular calcification. A large survey including 16 blood purification centers from 12 provinces in China identified male sex, age, DN, low hemoglobin, low albumin, and low serum calcium as risk factors associated with death in hemodialysis patients.²⁷ They also found that the hemodialysis patients preceding death had lower levels of DBP, serum phosphate, and Kt/V. However, according to the findings of our study, in the context of the COVID-19 pandemic, it is important to monitor oxygen saturation and recent cardiac damage in hemodialysis patients infected with SARS-COV-2, in addition to focusing on traditional risk factors for death.

In our study cohort, the median duration of viral shedding in survivors was 25 days from illness onset, but the virus was continuously detectable until death in nonsurvivors. The viral shedding period of our cohort is longer than that reported in general population (20 days),¹⁹ indicating the MHD population takes longer time to clear the virus. The prolonged viral shedding period might be attributed to the impaired immune system. The median time from illness onset to death in our cohort was 18 days, similar to 18.5 days in general population.¹⁵

In conclusion, our findings indicate that MHD patient is a highly vulnerable population at increased risk of mortality and prolonged virus shedding period in the ongoing COVID-19 pandemic. Advanced age, decreased oxygen saturation and low DBP on admission, as well as complications like acute cardiac injury developed during the clinical course are parameters associated with poor prognosis of COVID-19 in this population. These findings provide evidences for better administration and treatment strategies of COVID-19 patients and may help to reduce the mortality of MHD patients during the COVID-19 epidemic.

ACKNOWLEDGEMENTS

This study is based on data provided by Wuhan Hemodialysis Quality Control Center. All members of the 65 dialysis centers are appreciated.

CONFLICT OF INTEREST

The authors declare that they have no relevant financial interests.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: CZ, X-PM; drafted the manuscript: HT; analyzed data: J-BT, HT; collected data: CT, HT, C-TL, JL, ZZ, QY, XS. HT, CT, FX, XS, J-BT contributed equally to this work.

ETHICS APPROVAL

This study was approved by the Medical Ethics Committee of Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology (No. 2020-0071). Written informed consent was waived due to the rapid emergence of this infectious disease, and verbal consent was obtained from patients before enrollment.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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How to cite this article: Tang H, Tu C, Xiong F, et al. Risk factors for the mortality of hemodialysis patients with COVID-19: A multicenter study from the overall hemodialysis population in Wuhan. *Semin Dial*. 2022;35:71-80. <https://doi.org/10.1111/sdi.12995>