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Prognostic Factors for Mortality in Maintenance Hemodialysis Patients Infected with SARS-CoV-2

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Background: Maintenance hemodialysis patients are immunosuppressed, which increases their mortality risk if they contract coronavirus disease 2019 (COVID-19).

Methods: We studied data from 36 consecutive patients undergoing maintenance hemodialysis who were diagnosed as having COVID-19 from January 2020 to September 2023. Clinical data such as age and sex, laboratory data, radiological findings, modalities for blood purification therapy, and outcome at the time of discharge were collected from their hospital records. Binomial logistic regression analysis was used to predict risk factors for mortality and continuous hemodiafiltration (CHDF).

Results: After analyzing the correlation of outcomes with each prognostic factor, we identified 6 significant factors ($P < 0.05$). Age and initiation of CHDF were both associated with mortality. COVID-19 severity, steroid treatment, and serum lactate dehydrogenase level at admission were positively correlated with risk for CHDF initiation, while a greater number of vaccine doses was associated with lower risk.

Conclusions: Elderly hemodialysis patients have a higher mortality risk if they develop COVID-19 and require CHDF. More attention is warranted for vulnerable older patients with COVID-19 if they require hemodialysis. Risk reduction strategies, such as appropriate vaccination, are necessary.

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Key words: COVID-19, prognostic factor, mortality, maintenance hemodialysis, binary logistic regression model

Introduction

Patients receiving continuous renal replacement therapy (CRRT) are frequently immunosuppressed[1]. Among those receiving CRRT, patients on maintenance hemodialysis are particularly vulnerable. Several studies have examined mortality from coronavirus disease 2019 (COVID-19) in patients undergoing maintenance hemodialysis[2–4]. However, prognostic factors for mortality are unclear in SARS-CoV-2-infected patients undergoing maintenance hemodialysis. We investigated whether patient age, sex, laboratory and radiological findings at admission, COVID-19 severity, number of vaccine doses, and use of continuous hemodiafiltration (CHDF) were associated with outcomes.

Methods

Study Design

We retrospectively analyzed prognostic factors for mortality in maintenance hemodialysis patients with COVID-19. Potential prognostic factors derived from patients' characteristics, laboratory and radiological findings, and treatment regimens were entered into a binary logistic regression model.

Patients

We enrolled 36 consecutive SARS-CoV-2-infected patients on maintenance hemodialysis who were hospitalized at our hospital between January 2020 and September 2023.

Ethical Approval

This study adhered to the ethical standards of the Nip-

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pon Medical School Chiba Hokusoh Hospital (IRB approval number: H-2022-034) for all procedures involving human participants. It also complied with the principles of the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical standards.

Informed Consent

All participants included in this study provided written informed consent.

Outcome

The primary outcome was in-hospital death. The secondary outcome was CHDF during hospitalization.

Binary Logistic Regression Analysis

Evaluation of outcome

Death before discharge was assigned 1, and recovery at discharge was assigned 0 for the factor *Mortality*.

Evaluation of modalities for blood purification during hospitalization

Patients who underwent hemodialysis (HD) were assigned 1, while those who did not were assigned 0 for the factor HD. Patients who underwent CHDF were assigned 1, while those who did not were assigned 0 for the factor *CHDF*.

Evaluation of therapeutic agents for COVID-19 during hospitalization

Patients who received steroid treatment were assigned 1, while those who did not were assigned 0 for the factor *Steroid*. Patients who were treated with antiviral agents were assigned 1, while those who were not were assigned 0 for the factor *Antiviral*. Patients who received neutralizing antibodies were assigned 1, while those who did not were assigned 0 for the factor *Nab*. Patients who received antibiotics were assigned 1, while those who did not were assigned 0 for the factor *Antibiotics*.

Evaluation of COVID-19 severity

COVID-19 severity was evaluated by using the clinical guidelines advocated by Ministry of Health, Labour and Welfare of Japan. A mild case was defined as a saturation of percutaneous oxygen (SpO_2) greater than 96% and no respiratory symptoms and was assigned 1 for the factor *Severity*. A moderately severe (I) case was defined as an SpO_2 levels of >93% to <96% and presence of respiratory symptoms or pulmonary radiological findings and was assigned 2 for the factor *Severity*. A moderately severe (II) case was defined as an SpO_2 level of <93% or a need for oxygen and was assigned 3 for the factor *Severity*. A severe case was defined as a need for intensive care unit treatment or mechanical ventilation and was assigned 4 for the factor *Severity*.

Table 1 Clinical background of enrolled patients. Age is shown as mean ± SD. The mortality rate was calculated as the number of patients who died at discharge divided by the total number of enrolled patients. The distributions of primary causes of end-stage chronic kidney disease in enrolled patients are shown with the abbreviations below

Total, *n*		36
Age (yrs.) (mean ± SD)		63.6 ± 17.4
Gender, n (%)	male	28 (78)
	female	8 (22)
Mortality (Death/Total), %		(9/36), 25
DKD (Case/Total), %		(20/36), 56
CGN (Case/Total), %		(5/36), 14
NS (Case/Total), %		(7/36), 19
Others (Case/Total), %		(4/36), 11

DKD: diabetic kidney disease, CGN: chronic glomerulonephritis, NS: nephrosclerosis, Others: other causes.

Dose number of vaccinations

The number of vaccine doses administered before hospitalization was recorded and reflected in the factor *Vaccination*.

Laboratory findings on admission

Data from blood samples collected at admission, including lactate dehydrogenase (LDH), D-dimer, and C-reactive protein (CRP) levels, were analyzed to identify associations with mortality and CHDF.

Characteristics of Enrolled Patients

Sex

Female patients were assigned 1, while male patients were assigned 2.

Duration of HD initiation

Duration of HD treatment at discharge was calculated for each patient.

Past history

Patients with a history of cardiovascular disease were assigned 1, while those without were assigned 0 for the factor *Cardiovasc*. Patients with a history of respiratory disease were assigned 1, while those without were assigned 0 for the factor *Resp*. Patients with a history of liver disease were assigned 1, while those without were assigned 0 for the factor *Liver*.

Statistical analysis

All analyses were performed by using R version 4.0.0 (R Core Team, 2020) and IBM SPSS Statistics version 29.

Table 2 Clinical features of patients described in the Methods section

No.	age (yrs.)	gender	duration (yr.)	Cardiovasc.	Resp.	Liver
1	48	2	9.80	0	0	0
2	86	2	0.25	0	0	0
3	31	2	2.30	0	0	0
4	104	1	12.00	0	0	0
5	71	1	1.00	1	1	0
6	71	2	1.30	1	0	0
7	64	1	25.80	0	0	0
8	57	2	0.02	0	0	0
9	59	2	0.08	1	0	0
10	70	1	0.02	1	0	0
11	61	2	2.30	0	0	0
12	56	2	0.03	0	0	0
13	21	1	0.06	0	0	0
14	56	2	0.30	0	0	0
15	86	2	1.50	1	0	0
16	72	2	0.09	1	1	0
17	85	1	0.07	1	0	0
18	70	2	0.17	0	0	0
19	73	2	1.90	1	0	0
20	70	2	10.80	1	0	1
21	48	2	1.00	1	0	0
22	73	2	1.90	1	1	0
23	35	2	0.04	1	0	0
24	71	2	2.30	1	0	0
25	78	2	3.80	1	0	0
26	70	2	27.50	1	0	0
27	79	1	6.80	1	0	0
28	36	2	0.30	0	0	0
29	54	1	17.80	1	0	0
30	64	2	10.20	1	0	0
31	62	2	4.50	0	0	0
32	51	2	0.10	0	0	0
33	62	2	0.11	0	0	0
34	79	2	0.12	0	0	0
35	79	2	2.00	0	1	0
36	38	2	0.10	0	0	0

Abbreviations: duration (yr.): duration of HD initiation, Cardiovasc.: cardiovascular disease, Resp.: respiratory disease, Liver: liver disease.

A binomial logistic regression model was used to determine the association of each clinical characteristic with mortality in our sample. We used the same model to determine the extent to which each clinical characteristic served as a risk factor for initiation of CHDF. A P value of < 0.05 was considered to indicate statistical significance.

Results

Clinical Background of Enrolled Patients

A total of 36 consecutive patients were enrolled between January 2020 and September 2023. **Table 1** shows the background characteristics of these patients, including age, mortality rate, and distributions by sex and primary causes of end-stage chronic kidney disease. The clinical characteristics during hospitalization described in the Methods section are shown in **Table 2, 3**.

Assessment of Risk Factors for Mortality

Age and CHDF were associated with mortality. The relationship between the primary outcome and age, and initiation of CHDF, as determined by binary logistic regression analysis, is indicated by the formula (**Table 4**):

Table 3 Clinical information during hospitalization of each patient

No.	Mortality	HD	CHDF	steroid	antivirus	Nab	antibiotics	grade	Vac.	LDH	Ddi	CRP
1	0	1	0	1	1	0	1	2	0	286	0.8	8.72
2	1	1	0	1	0	0	1	2	0	250	10.5	6.66
3	0	1	0	0	1	1	0	1	2	200	0.8	0.96
4	1	1	0	1	1	1	0	3	2	199	3.1	1.48
5	0	1	0	0	1	1	0	1	2	231	0.7	0.83
6	0	1	0	0	1	1	0	2	3	263	2.9	5.95
7	0	1	0	1	0	0	1	1	0	208	0.8	0.59
8	1	0	1	1	1	0	1	1	0	251	1	14.46
9	1	0	1	1	1	0	1	4	0	668	1.6	9.15
10	1	0	1	1	1	0	1	3	0	260	14.2	4.93
11	0	1	0	1	1	0	1	2	0	163	1.4	0.78
12	1	1	1	1	1	0	1	4	0	703	4.7	8.67
13	0	1	1	0	0	0	1	4	0	766	41.8	39.06
14	0	1	1	1	1	1	1	4	0	526	87.4	8.46
15	0	1	0	1	1	1	1	3	0	283	0.7	6.98
16	1	0	1	1	0	1	1	4	2	581	2.9	12.86
17	1	0	1	1	0	1	1	4	3	1,081	33	9.51
18	0	1	1	0	1	1	1	1	0	198	1.5	0.64
19	0	1	0	0	1	1	0	2	0	316	0.6	9.52
20	0	1	0	0	1	1	1	2	3	418	4.1	11.01
21	0	1	0	0	0	0	1	1	0	205	1.6	10.04
22	0	1	0	0	1	1	0	1	3	216	1.5	1.88
23	0	1	1	1	1	0	1	3	0	340	1.8	12.82
24	0	1	0	0	0	0	1	1	1	122	2.1	12.03
25	0	1	0	0	1	0	0	1	4	196	3	5.33
26	0	1	0	0	1	0	1	1	4	172	1.7	0.14
27	0	1	0	0	0	0	1	1	4	140	3.4	20.11
28	0	1	0	0	0	1	1	1	2	851	4.6	3.8
29	0	1	0	0	0	0	1	1	1	143	2.8	22.62
30	0	1	0	0	0	0	1	1	3	192	0.1	7.36
31	0	1	0	0	1	0	1	1	2	759	24.9	32.17
32	0	1	0	0	0	0	1	2	4	455	2.9	9.39
33	0	1	0	0	1	0	0	1	4	231	3.4	4.88
34	0	1	0	0	1	0	0	0	5	239	18.8	3.87
35	1	1	0	1	1	0	0	4	5	542	29.9	42.09
36	0	1	0	0	0	0	1	2	3	527	3.3	2.85

HD: hemodialysis, CHDF: continuous hemodiafiltration, Nab: neutralizing antibodies, Vac.: number of vaccine doses, LDH: lactate dehydrogenase (IU/L), Ddi: D-dimer (μg/mL), CRP: C-reactive protein (mg/dL).

Table 4 Coefficients and constants in formula related to the mortality–age relationship, as well as the use of continuous hemodiafiltration

factor	coefficient	*P**
CT	2.610	0.021
constant	–2.833	0.006

CHDF: continuous hemodiafiltration.

Mortality = 0.163 × age + 5.283 × CHDF − 14.354

Assessment of Risk Factors for CHDF Initiation

The relationship between initiation of CHDF and COVID-19 severity was represented by a statistically significant formula containing a coefficient and a constant, as shown below (**Table 5a**).

CHDF = 1.359 × grade − 4.126

Similarly, the association of CHDF initiation with steroid treatment and serum LDH level at admission was represented by a statistically significant formula with coefficients and a constant, as shown below (**Table 5b**).

CHDF = 2.567 × steroid + 0.005 × LDH − 4.366

Furthermore, the association between initiation of CHDF and serum LDH level at admission, as well as the number of vaccine doses, was represented by a statistically significant formula with coefficients and a constant,

Table 5 Coefficients and constants included in a formula using binomial logistic regression analysis. a: Coefficient and constant in the formula for the relationship between initiation of continuous hemodiafiltration and COVID-19 severity. b: Coefficients and constant in the formula for the relationship between initiation of continuous hemodiafiltration and administration of steroids, and serum lactate dehydrogenase level. c: Coefficients and constant in the formula related to the relationship between the initiation of continuous hemodiafiltration and serum lactate dehydrogenase level, as well as the number of vaccine doses

a

factor	coefficient	*P**
grade	1.359	0.002
constant	–4.126	<0.001

b

factor	coefficient	*P**
steroid	2.567	0.017
LDH	0.005	0.029
constant	–4.366	0.003

c

factor	coefficient	*P**
LDH	0.008	0.022
vaccination	–1.746	0.049
constant	–2.487	0.029

LDH: lactate dehydrogenase.

as shown below (**Table 5c**).

CHDF = 0.008 × LDH − 1.746 × vaccination − 2.487

The figure illustrates these correlations and demonstrates the coefficients included in the formula for the association of clinical characteristics with mortality and CHDF.

Clinical Characteristics Not Associated with Mortality or CHDF Initiation in Patients with COVID-19

Gender, initiation of HD, therapeutic agents for COVID-19, D-dimer and CRP levels at admission, duration of initiation of HD at discharge, and history of cardiovascular, respiratory, and liver disease were not associated with mortality (**Table 6a**).

Gender, initiation of HD, therapeutic agents for COVID-19, excluding steroids, D-dimer, CRP at admission, duration of initiation of HD at discharge, and history of cardiovascular, respiratory, and liver disease were not associated with CHDF initiation (**Table 6b**).

Discussion

This study investigated whether clinical characteristics were associated with mortality in patients with COVID-19 who were receiving maintenance hemodialysis. Patients on maintenance hemodialysis are classified as immunocompromised hosts[1], and their mortality rate is higher than that of healthy people hospitalized for SARS-CoV-2 infection. In previous studies, the mortality rate associated with COVID-19 ranged from 24% to 32% in patients undergoing maintenance hemodialysis[2–4]. In the present study, the mortality rate was 25.0%, with 9 deaths among the 36 enrolled patients (**Table 1**). However, it is unclear which clinical characteristics are associated with mortality in patients undergoing maintenance hemodialysis.

We used a binomial logistic regression model to assess the extent to which each clinical characteristic was a risk factor for mortality during hospitalization for COVID-19. Li et al.[2] found that underlying respiratory disease increased mortality risk. Our findings show that COVID-19 severity, including SpO_2 and radiological findings in the lungs, was associated with initiation of CHDF.

Steroid treatment and a high serum LDH level at admission were associated with an elevated risk of CHDF initiation, whereas a greater number of vaccine doses was associated with lower risk (**Table 5b, c**).

There are various reasons why we chose the present clinical factors to assess the risk for initiation of CHDF. CHDF is preferred for critically ill patients. Pulmonary radiological findings at admission are used to classify COVID-19 severity. LDH is a cytoplasmic enzyme found in almost every organ, and serum LDH reflects destruction of damaged organs in critically ill patients. Furthermore, steroids are likely to be used to treat severe respiratory symptoms associated with COVID-19. Therefore, we hypothesized that more-severe COVID-19, use of steroid treatment, and elevated serum LDH at admission would be associated with higher risk for CHDF initiation (**Table 5**).

As compared with healthy people, patients on maintenance hemodialysis produce fewer antibodies for SARS-CoV-2 in response to vaccination[5–7]. Nonetheless, we found an inverse association between number of vaccine doses and initiation of CHDF (**Table 5c**), indicating that vaccination reduced the need for CHDF.

Elderly patients are also classified as immunocompromised hosts. In the present study, age and initiation of CHDF were associated with mortality (**Table 4**). Thus, elderly patients on maintenance hemodialysis requiring CHDF have a worse prognosis than others during hospitalization. COVID-19 severity was associated with greater

Table 6 Coefficient and constant included in a formula by binomial logistic regression analysis. a: Coefficients and constant in the formula related to the relationship between mortality and gender, initiation of hemodialysis, therapeutic agents for COVID-19, serum levels of D-dimer and C-reactive protein, duration of initiation of HD at discharge, and histories of cardiovascular, respiratory, and liver disease. b: Coefficients and constant in the formula related to the relationship between the initiation of continuous hemodiafiltration and gender, initiation of hemodialysis, therapeutic agents for COVID-19, excluding steroids, serum levels of D-dimer and C-reactive protein, duration of HD at discharge, and histories of cardiovascular, respiratory, and liver disease

a

factor	coefficient	P
gender	–15.472	1.000
HD	–97.055	0.997
steroid	78.379	0.997
antivirus	–32.841	0.999
Nab	20.566	1.000
antibiotics	–52.692	0.999
Ddi	–3.508	0.999
CRP	4.150	0.997
duration	–5.031	0.998
Cardiovasc.	–61.438	0.996
Resp.	29.564	1.000
Liver	124.150	0.998
constant	132.075	0.999

b

factor	coefficient	P
gender	–48.191	0.999
HD	–60.398	0.999
antivirus	47.097	0.996
Nab	–2.058	1.000
antibiotics	44.297	0.998
Ddi	–0.047	1.000
CRP	1.125	0.998
duration	–16.581	0.993
Cardiovasc.	–17.718	0.997
Resp.	–7.988	1.000
Liver	144.869	0.997
constant	85.980	0.999

HD: hemodialysis, Nab: neutralizing antibodies, Ddi: D-dimer, CRP: C-reactive protein, Cardiovasc.: cardiovascular disease, Resp.: respiratory disease, Liver: liver disease.

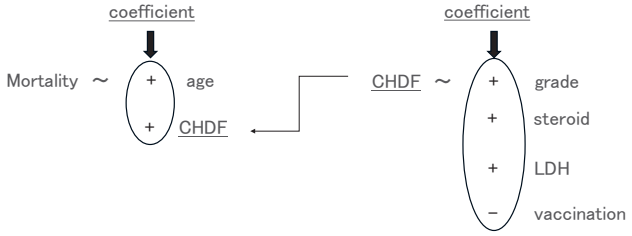

Fig. 1 Illustration of the coefficients included in the formula for the association of clinical characteristics with mortality and initiation of CHDF. Significant correlations are shown.
+ denotes positive number, – denotes negative coefficients.

risk for CHDF initiation (**Table 5a**). COVID-19 severity reflects pulmonary radiological findings and SpO_2, indicating that critical respiratory disease is a risk factor for CHDF initiation and increased mortality in elderly hemodialysis patients. Vaccination is recommended to reduce the risk of initiation of CHDF and decrease mortality (**Fig. 1**).

Doher et al.[8] reported that elevated D-dimer, LDH, and CRP levels were associated with the need for renal replacement therapy in COVID-19 patients. Similarly, LDH was linked to the initiation of CHDF in our current study (**Table 5b, c**). Nonetheless, D-dimer and CRP were not associated with initiation of CHDF or mortality (**Table 6a, b**). Thus, LDH was the only laboratory finding associated with the outcome in our current study.

Steroid therapy was associated with initiation of CHDF but not mortality (**Table 5b, 6a**). Other treatment options, such as antiviral drugs, neutralizing antibodies, and antibiotics, were not associated with initiation of CHDF or mortality (**Table 6a, b**). These findings suggest that older immunocompromised patients undergoing hemodialysis are at increased risk of mortality, even when receiving intensive treatments such as steroids and CHDF, when they have severe COVID-19. These findings were not affected by duration of HD or previous history of cardiovascular, respiratory, and liver disease (**Table 6a, b**).

Limitations

The current study enrolled a small number of patients. The number of vaccine doses was likely lower in early enrollees than in late enrollees. Thus, their immunologi-

cal status differed from that of late enrollees.

Conclusions

Elderly outpatients undergoing maintenance hemodialysis are at high risk for mortality if they have COVID-19 and require CHDF. COVID-19 severity, steroid treatment, and serum LDH levels at admission were associated with greater risk for initiation of CHDF. More attention is warranted for vulnerable patients with COVID-19, and risk reduction strategies, such as appropriate vaccination, are mandatory.

Conflict of Interest: None declared.

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