Original Article

KIDNEY RESEARCH AND CLINICAL PRACTICE

COVID-19–related clinical outcomes among Korean hemodialysis patients

Hayne Cho Park[1,2], Young-Ki Lee[1,2], Eunsil Ko[3], Sungbong Yu[4], AJin Cho[1,2], Do Hyoung Kim[1,2], Jinseog Kim[5], Jang-Hee Cho[6], Jeonghwan Lee[7], Dong Ki Kim[7], Seong Nam Kim[8], Chul-Woo Yang[9];
on behalf of the Korean Society of Nephrology COVID-19 Task Force Team

[1]Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea
[2]Hallym Kidney Research Institute, Hallym University College of Medicine, Seoul, Republic of Korea
[3]National Emergency Medical Center, National Medical Center, Seoul, Republic of Korea
[4]Department of General Surgery, Good Samaritan Bagae Hospital, Pyeongtaek, Republic of Korea
[5]Department of Bigdata and Applied Statistics, Dongguk University, Gyeongju, Republic of Korea
[6]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea
[7]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
[8]Kim Seong Nam Internal Medicine Clinic, Seoul, Republic of Korea
[9]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Background: Hemodialysis (HD) patients are more vulnerable to viral epidemics, experiencing higher mortality rates compared to individuals without chronic kidney disease (CKD). This retrospective cohort study sought to demonstrate clinical outcomes and associated factors among coronavirus disease 2019 (COVID-19) confirmed Korean HD patients.

Methods: From February 2020 to November 2021, the COVID-19 Task Force Team collected clinical data for HD patients with confirmed COVID-19 via a self-report survey of nephrologists. The composite outcome included in-hospital mortality, admission to the intensive care unit (ICU), and use of mechanical ventilation. Risk factors associated with clinical outcomes were analyzed among HD patients and compared to those of individuals without CKD using the COVID-19 database from the Korea Disease Control and Prevention Agency.

Results: A total of 380 HD patients from 206 facilities were diagnosed with COVID-19. Fever (49.5%) and cough (25.7%) were the two most common initial symptoms. The overall in-hospital fatality rate was 22.4% and even higher among ICU admission cases (64.7%). Non-survivors were older, more frequently developed shortness of breath, and were more likely to come from a nursing hospital. Compared to the age- and sex-matched non-CKD population, HD patients showed greater risk of in-hospital mortality (hazard ratio, 2.07; 95% confidence interval, 1.56–2.75; p < 0.001) and composite outcome (hazard ratio, 3.50; 95% confidence interval, 2.56–4.77; p < 0.001).

Conclusion: HD patients have a greater risk of in-hospital mortality and morbidity from COVID-19. Special attention should be paid to COVID-19 HD patients when they are older or present with symptoms.

Keywords: COVID-19, Dialysis, Mortality, Risk factors

Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has affected nearly 4 billion people to date and caused about 6 million deaths worldwide. Previous reports have determined that old age, comorbidities, and an immunocompromised state can increase the risk of death from COVID-19 [1–3]. Moreover, patients with end-stage renal disease exhibit a higher mortality rate compared to the general population. A study by a Belgian group recently reported the incidence, outcome, and mortality burden of SARS-CoV-2 infection in the Flemish region. They documented higher incidence (5.3% vs. 0.6%) and mortality (29.6% vs. 15.3%) rates among patients receiving hemodialysis (HD) compared to the general population [4]. Other recent studies from other countries have determined the mortality rate of HD patients to be around 30% [5–7].

Meanwhile, the COVID-19 Task Force Team, established under the Korean Society of Nephrology at the beginning of the COVID-19 pandemic, has developed COVID-19 prevention guidelines for HD units [8,9]. Thanks to the adherence to stringent primary prevention strategies in Korea, the overall fatality rate of COVID-19 in the general population has been lower than that in other countries (0.8% vs. 1.5%) [10]. However, no study has evaluated the mortality rate using a nationwide cohort database among HD patients in Korea. Therefore, this study evaluated the in-hospital fatality rate among Korean HD patients with a COVID-19 diagnosis and compared it to that of patients without chronic kidney disease (CKD). We also analyzed risk factors associated with in-hospital fatality among COVID-19–positive HD patients.

Methods

This study was approved by the Institutional Review Board of Hallym University Kangnam Sacred Heart Hospital (No. HKS 2021-07-013). The need to gather informed consent was waived due to the retrospective nature of the study.

Data collection

From February 2020 to November 2021, clinical infor-

mation as well as clinical outcomes of confirmed cases of COVID-19 were collected from each HD unit every 6 months using a nationwide survey. The survey was sent to each nephrologist to fill up the data, then returned to the Korean Society of Nephrology COVID-19 Task Force Team by e-mail. The clinical information of interest included patient age and sex; location and date of diagnosis; presence and type of initial symptoms; duration of hospitalization; admission to the intensive care unit (ICU); and use of mechanical ventilation (MV), continuous renal-replacement therapy, or extracorporeal membrane oxygenation. We also collected data about the type of dialysis unit and the presence of a nephrologist on staff at the dialysis unit.

We used the Korean COVID-19 nationwide database available from Korea Disease Control and Prevention Agency (KDCA) and excluded data of patients with CKD to compare clinical outcomes between the non-CKD population and HD patients. Among 5,628 patients confirmed to have COVID-19 up to April 30, 2020, a total of 5,570 patients were included in the current analysis as control subjects after excluding 58 patients with CKD.

Clinical outcome

First, we analyzed the in-hospital mortality rate and associated risk factors among HD patients confirmed to have COVID-19. Then, we compared the in-hospital fatality rate and composite outcome between HD patients and non-CKD patients. The composite outcome included in-hospital mortality, ICU admission, or MV application.

Statistical analyses

Statistical analyses were performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). The overall in-hospital fatality rate was calculated as the number of fatalities during hospitalization/total number of admitted patients. Clinical factors were compared between survivors and deceased patients using the chi-square test and independent t test. Kaplan-Meier curves were used to show the predicted survival between groups. A Cox proportional hazards model was used to demonstrate independent risk factors for mortality after adjusting other factors. A p-value of <0.05 was

considered statistically significant.

To compare the rate of in-hospital fatality and the composite outcome between non-CKD and HD patients, we performed propensity score matching (PSM). Age and sex were used for matching. The HD group was matched with the non-CKD group at a ratio of 1:3. In these matched cohorts, comparisons between groups were conducted with a paired t test, McNemar test, and the Wilcoxon signed-rank test. We conducted a multivariable Cox regression analysis to determine whether HD was an independent risk factor for in-hospital mortality and the composite outcome. Model 1 included only age, sex, and HD, and model 2 included the presence of initial symptoms in addition to the variables included in model 1.

Results

Clinical outcome among COVID-19–positive hemodialysis patients

A total of 380 HD patients from 206 facilities were diagnosed with COVID-19 until November 15, 2021. The mean age of these HD subjects was 66 years, with a male predominance (61.4%). About 2/3 of the patients were symptomatic upon initial diagnosis. Fever (49.5%) and cough (25.7%) were the most common presenting symptoms (Table 1). A total of 85 patients died among the 380 HD patients during 21.7 ± 14.9 days of hospitalization. The overall in-hospital fatality rate was 22.4% and even higher among those who were admitted to the ICU (64.7%). Non-survivors were older (73.0 ± 11.9 years vs. 64.3 ± 12.7 years, p < 0.001) and more likely to have received HD therapy from a nursing hospital (37.3% vs. 20.8%, p < 0.001). Non-survivors presented with shortness of breath more frequently (43.6% vs. 17.4%, p < 0.001) and a sore throat less frequently (2.6% vs. 10.0%). The in-hospital fatality rate did not differ according to the presence of a nephrology specialist on staff at the HD unit.

The composite outcome occurred in 121 patients (31.8%), stratified as 85 deaths, 102 admissions to ICU, and 49 cases of MV. A total of 45 patients received continuous renal-replacement therapy, and five patients received extracorporeal membrane oxygenation. The patients with the composite outcome were older (70.2 ± 12.9 years vs. 64.4 ± 12.7 years, p < 0.001) (Supplementary Table 1, available online). In addition, there were greater portions of symptomatic patients (77.9% vs. 59.7%, p = 0.001) among those with composite outcome, especially fever (61.9% vs. 42.7%, p =

Table 1. Factors associated with in-hospital mortality among hemodialysis patients with COVID-19

Factor	Total	Survivor	Non-survivor	p-value
No. of patients	380	295	85	
Age (yr)	66.2 ± 13.0	64.3 ± 12.7	73.0 ± 11.9	<0.001
Male sex	231 (61.4)	181 (62.2)	50 (58.8)	0.57
Symptom	211 (66.1)	152 (63.1)	58 (74.4)	0.07
Fever	158 (49.5)	113 (46.9)	45 (57.7)	0.10
Cough	82 (25.7)	60 (24.9)	22 (28.2)	0.56
Sputum	44 (13.8)	30 (12.4)	14 (17.9)	0.22
Sore throat	26 (8.2)	24 (10.0)	2 (2.6)	0.04
Rhinorrhea	16 (5.0)	15 (6.2)	1 (1.3)	0.13
Shortness of breath	76 (23.8)	42 (17.4)	34 (43.6)	<0.001
Loss of consciousness	6 (1.9)	3 (1.2)	3 (3.8)	0.16
Hospital type				<0.001
Private clinic	161 (43.4)	141 (49.0)	20 (24.1)	
Nursing hospital	91 (24.5)	60 (20.8)	31 (37.3)	
University hospital	60 (16.2)	43 (14.9)	17 (20.5)	
Others	59 (15.9)	44 (15.3)	15 (18.1)	
Presence of a nephrology specialist	290 (78.8)	229 (80.6)	61 (72.6)	0.11

Data are expressed as number only, mean ± standard deviation, or number (%).
COVID-19, coronavirus disease 2019.
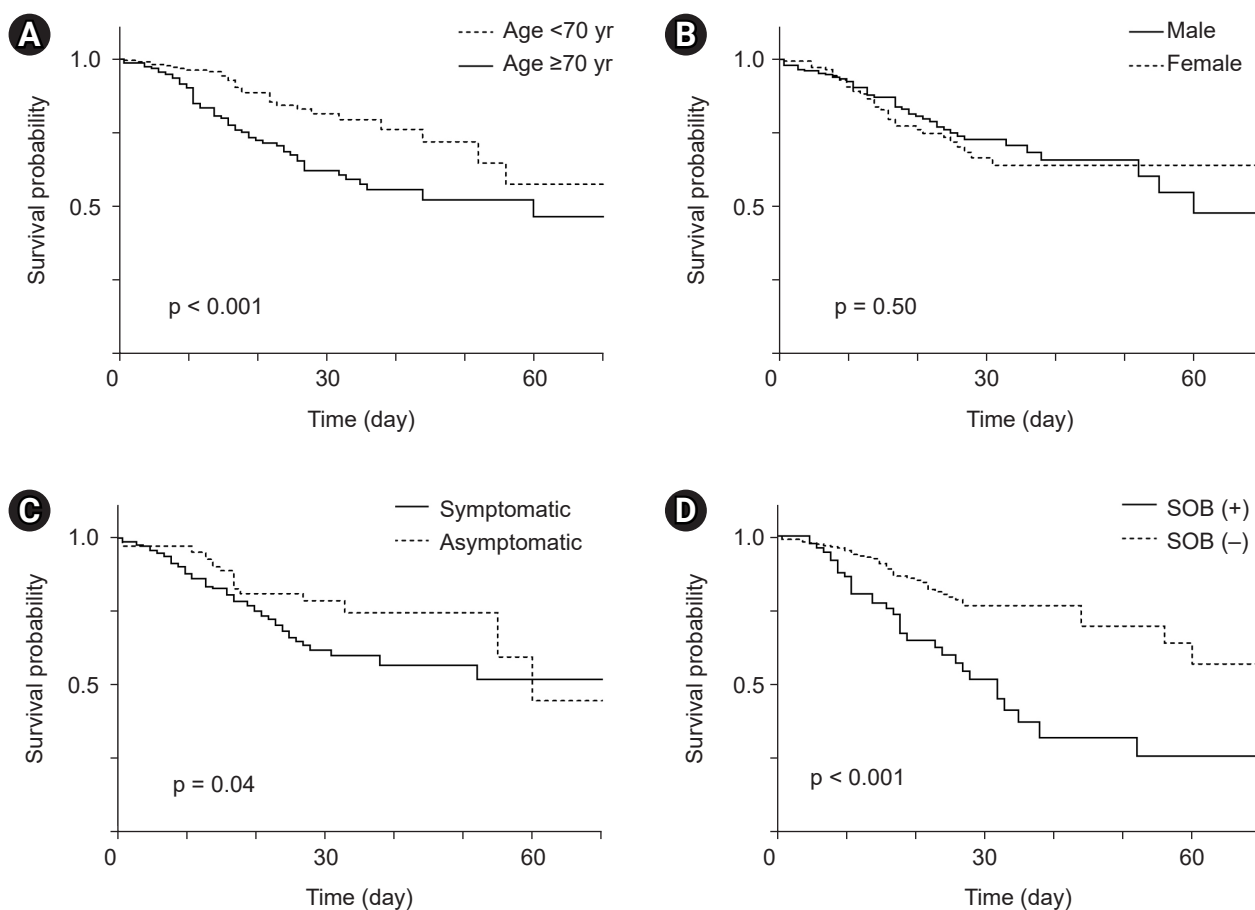
0.001), sputum (18.6% vs. 11.2%, p = 0.07), and shortness of breath (42.5% vs. 13.6%, p < 0.001).

Risk factors associated with in-hospital fatality among COVID-19–positive hemodialysis patients

We analyzed the risk factors for in-hospital mortality among HD patients (Fig. 1). Those patients aged ≥70 years old demonstrated a greater risk of death during hospitalization (log-rank test, p < 0.001) (Fig. 1A). The mortality rate did not differ between male and female patients (log-rank test, p = 0.50) (Fig. 1B). Symptomatic patients experienced poorer survival compared to asymptomatic patients (log-rank test, p = 0.038) (Fig. 1C). Among specific symptoms, shortness of breath was the only significant symptom re-

lated to in-hospital mortality (log-rank test, p < 0.001) (Fig. 1D).

When we performed the univariate Cox regression analysis, patient age, the presence of initial symptoms, and shortness of breath were associated with in-hospital mortality (Table 2). We then performed multivariate Cox proportional modeling to define independent risk factors for in-hospital mortality. When we adjusted patient age, sex, and the presence of symptoms (model 1), the risk of death increased by 1.5 times as the age increased by 10 years (p < 0.001), and initially symptomatic patients showed a 72% higher risk of death compared to asymptomatic patients (p = 0.04). When we adjusted patient age; sex; and the presence of fever, sore throat, and shortness of breath in model 2, age (hazard ratio [HR], 1.433; 95% confidence interval

Figure 1. Risk factors associated with in-hospital death among COVID-19–positive hemodialysis patients. (A) The patients aged ≥70 years showed a higher mortality rate compared to younger patients (p < 0.001). (B) The mortality rate did not differ according to sex. (C) Patients with initial COVID-19–related symptoms showed a poorer survival rate compared to asymptomatic patients (p = 0.04). (D) Among various COVID-19–related symptoms, SOB was the only independent factor associated with in-hospital mortality (p < 0.001). COVID-19, coronavirus disease 2019; SOB, shortness of breath.

Table 2. Cox proportional hazards model for in-hospital fatalities among hemodialysis patients

Variable	Unadjusted		Model 1[a]		Model 2[b]	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (/10 yr)	1.50 (1.23–1.82)	<0.001	1.50 (1.22–1.85)	<0.001	1.43 (1.17–1.76)	0.001
Male sex (vs. female)	0.86 (0.56–1.33)	0.51	0.94 (0.59–1.50)	0.80	0.79 (0.49–1.26)	0.33
Nursing hospital (vs. others)	1.31 (0.84–2.06)	0.24	–	–	–	–
Symptomatic (vs. asymptomatic)	1.71 (1.02–2.88)	0.04	1.73 (1.03–2.91)	0.04	–	–
Fever (vs. none)	1.49 (0.95–2.34)	0.08	–	–	1.18 (0.73–1.89)	0.50
Sore throat (vs. none)	0.30 (0.07–1.24)	0.10	–	–	0.27 (0.06–1.11)	0.07
Rhinorrhea (vs. none)	0.26 (0.04–1.83)	0.17	–	–	–	–
Shortness of breath (vs. none)	2.80 (1.79–4.38)	<0.001	–	–	2.96 (1.82–4.82)	<0.001

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, and symptom status (vs. asymptomatic). [b]Adjusted for age, sex, fever, sore throat, and shortness of breath.

[CI], 1.168–1.759; p = 0.001) and the presence of shortness of breath (HR, 2.964; 95% CI, 1.824–4.816; p < 0.001) were independently related to in-hospital mortality.

The risks of in-hospital mortality and the composite outcome were higher in the hemodialysis population compared to the non-chronic kidney disease population

Clinical characteristics of 380 HD patients were compared to those of 5,570 non-CKD patients with a COVID-19 diagnosis (Table 3). The HD patients included a greater proportion of elderly and male patients, but the proportions of symptomatic patients were similar between the groups. Among symptomatic patients, fever, shortness of breath, and loss of consciousness occurred more frequently in HD patients, while cough, sputum, sore throat, and rhinorrhea were more frequently experienced by the non-CKD population.

HD patients showed a higher in-hospital fatality rate compared to that of the non-CKD population (22.4% vs. 4.1%, p < 0.001). The Kaplan-Meier curve showed a significantly lower 28-day in-hospital survival rate among HD patients compared to the non-CKD population (Fig. 2). To evaluate whether HD independently increased the mortality risk, we performed an age- and sex-matched multivariate Cox regression analysis. The baseline characteristics after PSM are presented in Supplementary Table 2 (available online). In the unadjusted Cox regression analysis, patient age, HD status, and an initially symptomatic status led to a higher risk of in-hospital mortality (Table 4). After adjusting other factors, HD status remained an independent risk factor for in-hospital death, leading to a two-fold higher

risk for death compared to that of the non-CKD population (HR, 2.07; 95% CI, 1.56–2.75; p < 0.001 in model 2). Patients receiving HD were at greater risk of death compared to non-CKD patients when considering only those aged <70 years (Fig. 3A). Both male and female HD patients showed a higher risk of death compared to their non-CKD counterparts (Fig. 3B).

The composite outcome occurred in 31.8% of the HD population and 6.0% of the non-CKD population, respectively (p < 0.001) (Table 3). When we performed a multivariate Cox regression analysis for the composite outcome (Table 4), HD status was the most potent risk factor for the composite outcome (HR, 3.50; 95% CI, 2.56–4.77; p < 0.001). In addition, HD status was an independent risk factor for ICU admission and MV application (Table 4).

Discussion

This is the first Korean nationwide cohort study to reveal the mortality risk and associated factors among COVID-19–confirmed HD patients. Our study revealed that the in-hospital fatality rate was higher among HD patients compared to non-CKD patients (22.4% vs. 4.1%). Old age and the presence of shortness of breath at initial presentation were associated with in-hospital fatality among HD patients. After adjusting for patient age and sex, the risk of in-hospital death was 2.1 times higher in HD patients compared to the non-CKD population. HD patients also had a 3.5-fold greater risk of the composite outcome compared to non-CKD patients.

Our study compared the clinical outcomes of HD pa-

Table 3. Comparison of clinical characteristics between non-CKD and HD patients with COVID-19

|	Total (n = 5,950)	Non-CKD (n = 5,570)	HD (n = 380)	p-value
Age group (yr)				<0.001
<10	66 (1.1)	66 (1.2)	0 (0)	
10–19	206 (3.5)	206 (3.7)	0 (0)	
20–29	1,116 (18.8)	1,116 (20.0)	0 (0)	
30–39	572 (9.6)	561 (10.1)	11 (2.9)	
40–49	771 (13.0)	738 (13.2)	33 (8.8)	
50–59	1,198 (20.1)	1,133 (20.3)	65 (17.3)	
60–69	1,019 (17.1)	909 (16.3)	110 (29.3)	
70–79	628 (10.6)	541 (9.7)	87 (23.2)	
≥80	369 (6.2)	300 (5.4)	69 (18.4)	
Male sex	2,522 (42.4)	2,291 (41.1)	231 (61.6)	<0.001
Symptom	3,956 (67.2)	3,745 (67.2)	211 (66.1)	0.73
Fever	1,443 (24.5)	1,285 (23.1)	158 (49.5)	<0.001
Cough	2,402 (40.8)	2,320 (41.7)	82 (25.7)	<0.001
Sputum	1,652 (28.1)	1,609 (28.9)	43 (13.5)	<0.001
Sore throat	905 (15.4)	879 (15.8)	26 (8.2)	<0.001
Rhinorrhea	634 (10.8)	618 (11.1)	16 (5.0)	<0.001
Shortness of breath	732 (12.4)	656 (11.8)	76 (23.8)	<0.001
Loss of consciousness	40 (0.7)	34 (0.6)	6 (1.9)	0.02
Clinical outcome				
In-hospital fatality	310 (5.2)	225 (4.0)	85 (22.4)	<0.001
ICU admission	280 (4.8)	178 (3.2)	102 (37.2)	<0.001
MV application	66 (1.1)	17 (0.3)	49 (18.0)	<0.001
Composite outcome	455 (7.7)	334 (6.0)	121 (31.8)	<0.001

Data are expressed as number (%).
CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; HD, hemodialysis; ICU, intensive care unit; MV, mechanical ventilation.

tients and non-CKD patients hospitalized with COVID-19. Kang et al. [11] also compared clinical outcomes between CKD and non-CKD patients using Korean national claims data; however, they only included 14 dialysis-dependent CKD patients. Another study by Jung et al. [12] analyzed outcomes of COVID-19 among patients on in-center HD, but it did not compare outcomes between HD and non-CKD patients. Moreover, these authors also included small numbers of HD patients. Therefore, our study is the first study to report the in-hospital mortality rate and associated factors among a large number of HD patients and to compare their clinical outcome with that of non-CKD patients. A previous investigation from the United States documented a higher in-hospital mortality rate among patients with end-stage renal disease compared to those without it (31.7% vs. 25.4%) [13]. Another study from China showed that the mortality rate in maintenance HD patients was as high as 39.2% [14]. Although it is difficult to compare

unadjusted mortality rates directly across nations, the lower in-hospital fatality rate among Korean HD patients may be due to strict prevention strategies and pre-symptomatic screening [1]. In addition, the COVID-19 Task Force Team was established under the Korean Society of Nephrology from the very beginning of the epidemic to prevent secondary transmission of SARS-CoV-2 among HD patients [9]. The COVID-19 Task Force Team not only published a COVID-19 prevention guideline [8] but also proposed adequate vaccination and treatment policies to the KDCA, which resulted in lower rates of disease incidence and mortality among HD units [15].

Previous studies have suggested the proportion of asymptomatic SARS-CoV-2 infection among HD patients is approximately 25% [16,17]. Our study demonstrated a higher prevalence of asymptomatic infection (33.9%) compared to previous studies. The reason for the higher prevalence of asymptomatic infection here would be the exten-
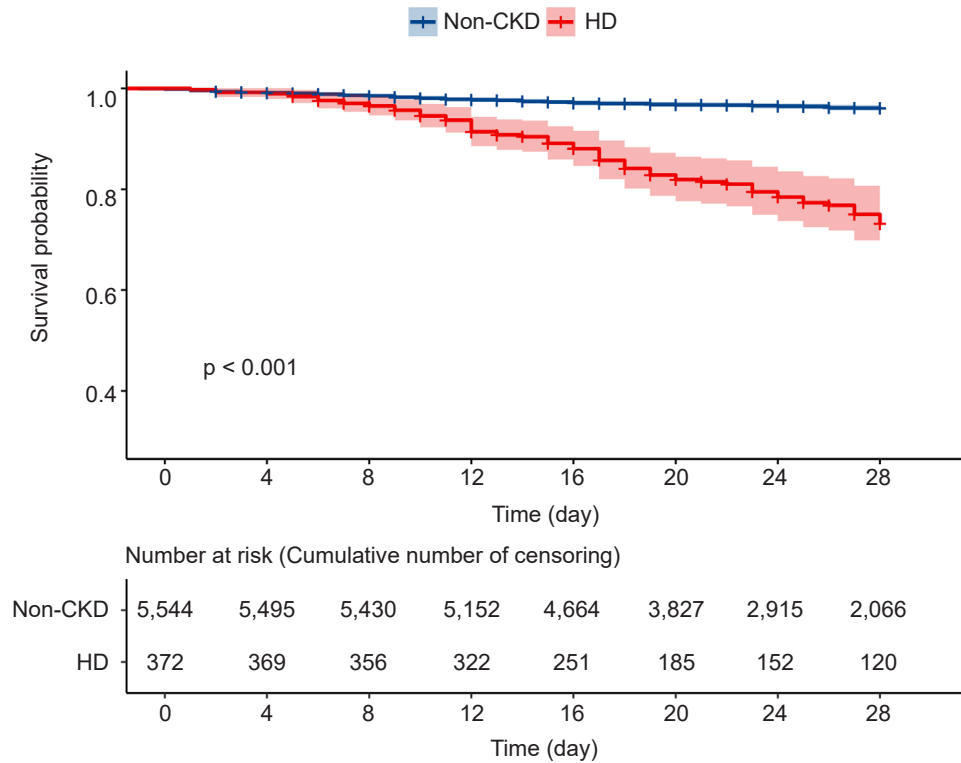
Figure 2. Kaplan-Meier survival curve comparing 28-day in-hospital fatality rates between HD patients and non-CKD patients. HD patients showed a higher in-hospital fatality rate compared to non-CKD patients (22.4% vs. 4.1%, p < 0.001). The Kaplan-Meier curve revealed a significantly lower 28-day in-hospital survival rate among HD patients compared to non-CKD patients (p < 0.001). CKD, chronic kidney disease; HD, hemodialysis.

Table 4. Cox regression analysis for clinical outcomes according to end-stage renal disease status

Variable	Outcome	Unadjusted		Model 1[a]		Model 2[b]	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
HD (vs. non-CKD)	In-hospital fatality	2.00 (1.51–2.63)	<0.001	1.90 (1.44–2.51)	<0.001	2.07 (1.56–2.75)	<0.001
	ICU admission	7.43 (5.33–10.37)	<0.001	7.97 (5.66–11.24)	<0.001	8.45 (5.91–12.08)	<0.001
	MV application	29.76 (13.89–63.76)	<0.001	30.41 (14.15–65.36)	<0.001	29.88 (13.86–64.42)	<0.001
	Composite outcome	2.53 (1.93–3.32)	<0.001	2.81 (2.11–3.75)	<0.001	3.50 (2.56–4.77)	<0.001

CI, confidence interval; CKD, chronic kidney disease; HD, hemodialysis; HR, hazard ratio; ICU, intensive care unit; MV, mechanical ventilation.
[a]Adjusted for age and sex. [b]Adjusted for model 1 + symptom status (vs. asymptomatic).

sive screening strategy of contact patients or patients under investigation [8]. Our previous report also demonstrated a higher prevalence of asymptomatic COVID-19 patients in the general population [18]. Although mortality rates between symptomatic and asymptomatic patients did not differ in the general population (4.5% vs. 3.3%, p = 0.017) [18], the in-hospital mortality rate was significantly higher for symptomatic patients compared to asymptomatic patients among those receiving HD (HR, 1.727; 95% CI, 1.025–2.912;

p = 0.04). As in previous studies, fever (49.5%) and cough (25.7%) were the most common symptoms among HD patients [5,19]. Our study revealed that old age and shortness of breath at initial presentation are the primary risk factors for in-hospital mortality among HD patients, while the presence of a sore throat is a protective factor. A recent study by Jang et al. [20] also demonstrated that dyspnea and altered mental status are high-risk symptoms, while rhinorrhea and headache are low-risk symptoms among
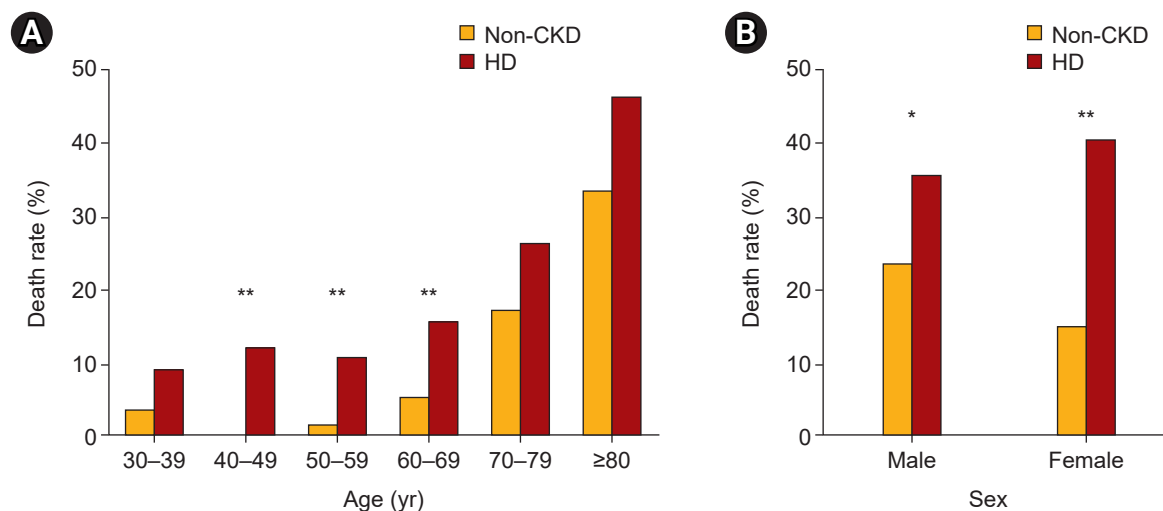
Figure 3. Comparison of in-hospital mortality rates between HD and non-CKD patients according to age and sex. (A) Patients aged 40 to 70 years on HD showed a significantly higher mortality rate than those in the non-CKD population. (B) Male and female HD patients showed higher mortality rates compared to those in the non-CKD population. *p < 0.05, **p < 0.001.
CKD, chronic kidney disease; HD, hemodialysis.

patients with COVID-19.

As seen in the general population, old age was the risk factor for patient mortality. Patients aged ≥70 years showed a high mortality rate in both the HD (35.3%) and non-CKD (24.4%) populations (p > 0.05). However, relatively younger patients aged 40 to 69 years showed a higher mortality rate among HD patients compared to the non-CKD population (Fig. 3A). This may be related to the greater presence of comorbidities, such as diabetes, cerebrovascular disease, or heart failure, among HD patients. Previous studies showed that age and the presence of comorbidities are the two most important risk factors for COVID-19–related mortality [1,3]. Unfortunately, we could not adjust comorbidities as the main confounders in our study since we did not collect comorbidity data through the survey.

Previous studies have demonstrated well that male patients experience poorer clinical outcomes compared to female patients [1,4,11]. Unlike in other studies, however, there was no difference in the mortality rate between sexes in our study. The possible explanation for this may be that our female patients were older than our male patients (68.4 ± 13.2 years vs. 64.8 ± 12.8 years, p = 0.009). Therefore, the male and female patients in our cohort may present different baseline characteristics that may diminish the mortality difference between sexes.

Our study has several limitations. First, we collected data using a survey, not via systematic data collection. Therefore, there are much missing data, especially on treatment modality and the presence of symptoms. In addition, we could not calculate the incidence of COVID-19 infection among HD patients since this study was not based on national registry data but instead on results of a self-report survey. Second, we only analyzed the in-hospital mortality rate but not the long-term overall mortality rate. In addition, the period of data collection differed between HD and non-CKD patients (January 2020 to April 2020 for the non-CKD population and February 2020 to November 2021 for HD patients). Since the dominant viral variant changed over time, the overall mortality rate in HD patients may be under-estimated. Third, we did not collect comorbidities or laboratory data, which are known to be major factors affecting patient mortality. Finally, we could not analyze the effect of vaccination since data about individual vaccination history were not collected during the study period.

In conclusion, HD patients have a higher risk of in-hospital mortality and severe COVID-19 outcomes. Older HD patients and those with initial symptoms should be more closely monitored.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

Authors' contributions

Conceptualization: HCP, YKL
Data curation: HCP, YKL, EK, SY, DHK, JHC, JL, DKK, SNK
Formal analysis: DHK, JK
Methodology: DHK, AJC
Writing–original draft: HCP
Writing–review & editing: YKL, CWY, EK, WY, AJC, DHK, JK, JHC, JL, DKK, SNK
All authors read and approved the final manuscript.

ORCID

Hayne Cho Park, https://orcid.org/0000-0002-1128-3750
Young-Ki Lee, https://orcid.org/0000-0003-3464-6144
Eunsil Ko, https://orcid.org/0000-0001-5959-5545
Sungbong Yu, https://orcid.org/0000-0002-1989-6121
AJin Cho, https://orcid.org/0000-0001-7097-7026
Do Hyoung Kim, https://orcid.org/0000-0002-8664-8830
Jinseog Kim, https://orcid.org/0000-0003-3172-3212
Jang-Hee Cho, https://orcid.org/0000-0002-7031-5214
Jeonghwan Lee, https://orcid.org/0000-0003-3199-635X
Dong Ki Kim, https://orcid.org/0000-0002-5195-7852
Seong Nam Kim, https://orcid.org/0000-0002-6986-1904
Chul-Woo Yang, https://orcid.org/0000-0001-9796-636X

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