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CLINICAL STUDY

The impact of COVID-19 infection before the vaccination era on the hospitalized patients requiring hemodialysis: a single-center retrospective cohort

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ABSTRACT

Due to effective vaccinations, the COVID-19 (coronavirus disease 2019) infection that caused the pandemic has a milder clinical course. We aimed to assess the mortality of hospitalized COVID-19 patients before the vaccination era. We investigated the mortality in those patients between 1 October 2020 and 31 May 2021 who received hemodialysis treatment [patients with previously normal renal function (nCKD), patients with chronic kidney disease previously not requiring hemodialysis (CKDnonHD), chronic kidney disease (CKD), and patients on regular hemodialysis (pHD)]. In addition, participants were followed up for all-cause mortality in the National Health Service database until 1 December 2021. In our center, 83 of 108 (76.9%) were included in the analysis due to missing covariates. Over a median of 26 (interquartile range 11–266) days of follow-up, 20 of 22 (90.9%) of nCKD, 23 of 24 (95.8%) of CKDnonHD, and 17 of 37 (45.9%) pHD patients died ($p < 0.001$). In general, patients with nCKD had fewer comorbidities but more severe presentations. In contrast, the patients with pHD had the least severe symptoms ($p < 0.001$). In a model adjusted for independent predictors of all-cause mortality (C-reactive protein and serum albumin), CKDnonHD patients had increased mortality [hazard ratio (HR) 1.91, 95% confidence interval (CI), 1.02–3.60], while pHD patients had decreased mortality (HR 0.41, 95% CI 0.20–0.81) compared to nCKD patients. After further adjustment for the need for intensive care, the difference in mortality between the nCKD and pHD groups became non-significant. Despite the limitations of our study, it seems that the survival of previously hemodialysis patients was significantly better.

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1. Introduction

The world was changed since December 2019; multiple cases of pneumonia caused by a novel coronavirus have been reported in Wuhan, Hubei province. The disease has spread quickly to many regions in China and other countries, such as Japan, Thailand, the United States, and Europe, with strong infectivity [1]. The most frequent clinical course of infection is asymptomatic cases and mild and nonspecific respiratory syndromes. A generalized and violent inflammatory response needing intensive care unit (ICU) assistance, mechanical ventilation, and occasionally renal replacement therapy is much less frequent [2]. The Centers for Disease Control guidance on SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) related states that while everyone is at risk of COVID-19 (coronavirus disease 2019), specific populations have an increased risk of severe illness, including older adults, individuals with CKD, individuals with chronic obstructive pulmonary disease, solid organ transplant recipients, those with obesity, cardiac conditions, and type 2 diabetes mellitus. Patients with end-stage kidney disease and those on dialysis are at particular risk, owing to both dysfunctions of innate and adaptive immunity and a significant burden of comorbid conditions (cardiac disorders and type 2 diabetes) [3,4]. Since the outbreak of COVID-19, many regulations have been achieved to control the disease, e.g., such as lockdowns and beginning vaccinations.

The all-cause mortality of COVID-19 patients requiring new-onset hemodialysis (HD) due to acute or acute-on-chronic kidney disease can be staggeringly high [5]. Before the era of vaccinations, patients undergoing dialysis were at

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a greater risk of hospitalization and death due to COVID-19 [6,7]. Patients on chronic HD treatment with a positive test for SARS-CoV-2 infection pose a further challenge: their regular transfer to the dialysis unit may facilitate the spread of the disease; hence, their threshold for hospital admission is lower. They are even hospitalized if they are asymptomatic [8]. This indication bias could lead to lower mortality among HD patients hospitalized with a positive SARS-CoV-2 test result. While chronic HD patients or kidney transplant recipients have been found to have high mortality rates, COVID-19 infected patients with acute kidney injury have reported extremely high mortality rates [9,10].

Given these controversies, we aimed to assess the mortality of hospitalized COVID-19 patients who received hemodialysis treatment (patients with previously normal renal function, patients with chronic kidney disease previously not requiring hemodialysis, and CKD patients on regular hemodialysis). Based on our analysis of the papers cited, we have developed a confident hypothesis that patients with a history of normal kidney function and those with chronic kidney disease who have not undergone hemodialysis previously are at a higher risk of all-cause mortality compared to those who regularly receive HD treatment. Although our study had some limitations, such as a small sample size and being conducted at a single center, it is crucial to emphasize that our results were obtained from a lengthy follow-up period and before the introduction of SARS-CoV-2 vaccination.

2. Materials and methods

2.1. Setting

As part of an ongoing cohort study of all hospitalized COVID-19 patients (≥18 years of age) at Semmelweis University, we retrospectively collected data on all patients with confirmed SARS-CoV-2 infection who received HD treatment between 1 October 2020 and 31 May 2021. According to the World Health Organization's interim guidelines, the diagnosis of SARS-CoV-2 infection is based on a positive antigen test confirmed by a polymerase chain reaction (PCR) test [11]. Baseline assessment and treatment of COVID-19 were performed in line with Semmelweis University treatment guidelines [12]. In brief, standardized forms on demographics, medical history, and presenting symptoms were completed, and a standard set of laboratory parameters was collected at the clinical admittance. Patients received supportive care (nasal oxygen, noninvasive or invasive ventilatory support, low molecular weight heparin in prophylactic doses, and dexamethasone in line with international guidelines); however, no remdesivir treatment was administered because the FDA product label does not recommend the use of remdesivir in patients with an eGFR of <30 mL/min. None of the study participants received vaccination against SARS-CoV-2 before hospitalization. Data on the need for mechanical ventilation and treatment in the intensive care unit (ICU) during hospitalization were also collected. In addition, participants were followed up for all-cause mortality in the National Health Service database until 1 December 2021.

All study-related procedures were performed by the 1964 Declaration of Helsinki's ethical standards and later amendments. Local ethical approval was obtained from the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (registration number SE-RKEB 245-1/2020). The Hungarian laws of the ethics committee waived the need for informed consent, as no specific study-related procedures were performed.

2.2. Participants

We included those patients in our cohort who required HD treatment during the new onset of SARS-Cov-2 infection [patients with previously normal renal function (nCKD), patients with chronic kidney disease previously not requiring hemodialysis (CKDnonHD), chronic kidney disease (CKD), and patients on regular hemodialysis (pHD)]. Out of 108 individuals in our center, 83 (76.9%) were eligible for analysis in the three groups, as some covariates were missing. These missing covariates mainly consisted of laboratory parameters. We did not enroll patients on peritoneal dialysis (PD) with primarily renal replacement therapy and excluded them if they moved to HD. Patients in the study were not vaccinated against COVID-19 infection because it was not yet generally available to patients at this time interval.

2.3. Predictors and covariates

At the clinical admittance, demographic and clinical data, vital signs, and symptoms were obtained from each participant's electronic medical records (EMR). In addition, from *demographic* characteristics, we collected information on the age and sex of the patients.

The following *comorbidities* were recorded in medical history: hypertension, ischemic heart disease (angina or prior myocardial infarction or history of revascularization), chronic obstructive pulmonary disease, treated diabetes mellitus (either type 1 or 2), and chronic kidney disease status. In addition, CKD was defined as an estimated glomerular filtration rate below 60 mL/min/1.73 m^2 based on at least two measurements at least three months apart up to 12 months before hospital admission [13,14]. Additionally, we gathered information on other medical conditions, such as immunization and malignant disease. However, we did not observe any noteworthy correlations with mortality.

Among *vital signs*, we included systolic and diastolic blood pressure (measured with an automated device) and oxygen saturation (based on pulse oximetry). The only *symptom* we used in the current analysis was dyspnea at presentation.

Laboratory data were collected directly from the hospital system and were measured in the same central laboratory (Central Laboratory of the Department of Laboratory Medicine, Semmelweis University) on automated systems. At hospital admission, we recorded blood cell counts and creatinine, high-sensitivity C-reactive protein (CRP), total protein, and albumin levels.

We also collected data on *intermediate outcomes*, including the need for mechanical ventilation and ICU placement during the initial hospitalization, as markers of COVID-19 severity.

2.4. Outcome

Hungary has a single-payer health insurance system covering most social and health-related activities. In the current report, all participants were flagged with their NHS ID in the NHS Masterfile, and their last known status was recorded as dead or alive. Follow-up started at the time of hospital admission and was censored at death or inactivation (due to expatriation) or at the end of follow-up (1 December 2021), whichever came first.

2.5. Statistical methods

Descriptive data were presented as numbers and percentages for categorical variables and mean ± standard deviation or median [interquartile range] for continuous variables. Normality tests and visual observation of histograms and Q–Q plots investigated the normality of continuous variables. Non-normally distributed variables were log-transformed as required.

Baseline data stratified by CKD status and living status at follow-up are presented. Comparisons between the CKD groups were made using the chi^2-test or one-way ANOVA, as appropriate. *p*-Values for both heterogeneity and trends were reported. For comparison by living status, chi^2-tests or 2-sample *t*-tests were performed.

Next, we fitted hierarchical Cox proportional hazards models to estimate the hazard ratios (HRs) with 95% confidence intervals (CI) for CKD status on all-cause mortality. The basal model (*Model 1*) was unadjusted. In subsequent models, we selected independent predictors of all-cause mortality by adding demographic variables (age and sex), anamnestic variables (congestive heart failure), and presenting signs and symptoms (dyspnea, oxygen saturation, diastolic blood pressure) and using a backward stepwise method, laboratory measures at presentation (white blood cell count, C-reactive protein, creatinine, and albumin). All variables that showed a univariate association with a *p*-value <0.10 were available for these models. *Model 2* shows how the relative risk of all-cause mortality was adjusted for the independent predictors selected through the previous process. Model 3 further added intermediate outcomes (the need for mechanical ventilation and ICU treatment) using a backward stepwise method.

For graphical representation, Kaplan–Meier survival curves (with a log-rank test) are presented according to CKD status and the survival function based on Model 2. We selected Model 2 over Model 3 because the intermediate outcomes were unknown at hospital admission, potentially leading to over-adjustment.

All analyses were performed on IBM SPSS Statistics version 28.0.

3. Results

3.1. Participants

Altogether,108 patients with COVID-19 required HD treatment during the study period. These 25 patients were excluded due to missing baseline covariates, and no patients were lost to follow-up. The final analytical sample comprised 83 patients: 22 with previously normal renal function (nCKD), 24 with chronic kidney disease previously not requiring hemodialysis (CKDnonHD), and 37 with CKD on regular hemodialysis (pHD) (Figure 1).

3.2. Baseline characteristics and intermediate outcomes by CKD status

The groups without CKD, those with CKD without prior HD treatment, and those on chronic HD treatment had similar age and sex distributions with male predominance. Patients without CKD had fewer comorbidities, with a lower frequency of hypertension, diabetes, and ischemic heart disease than patients with CKD with or without HD treatment. Due to the lower absolute risks, there were no differences in the prevalence of stroke, chronic obstructive pulmonary disease, or congestive heart failure (Table 1).

We found significant trends representing more severe signs and symptoms from patients without CKD through those with CKD not on chronic HD to those on regular HD in terms of the frequency of dyspnea, mean values of oxygen saturation, and diastolic blood pressure $p < 0.001$) (Table 1).

Laboratory values representing systemic inflammation also showed similar trends, with the highest white blood cell count and CRP values in the group without CKD and the lowest in the HD group. The markers known to be markers of CKD (such as hemoglobin and creatinine) showed trends accordingly. The serum albumin level was the lowest in the group without CKD and increased across the CKD groups ($p = 0.017$) (Table 1).

The need for mechanical ventilation and ICU treatment showed a strong trend, with lower rates among patients on HD and those with CKD not on chronic HD treatment ($p < 0.001$) (Table 1).

3.3. Baseline characteristics and intermediate outcomes by survival status

Deceased patients tended to be older, have congestive heart failure less frequently in their medical history, present more often with dyspnea, and have lower oxygen saturation (all $p < 0.001$). They had lower diastolic blood pressure, higher white blood cell count, higher CRP level, lower creatinine level, and lower albumin level at admission (all $p < 0.05$) (Table 2).

Regarding intermediate outcomes, almost none of the surviving patients required mechanical ventilation or ICU treatment, whereas more than half of the deceased patients required these procedures ($p < 0.001$) (Table 2).

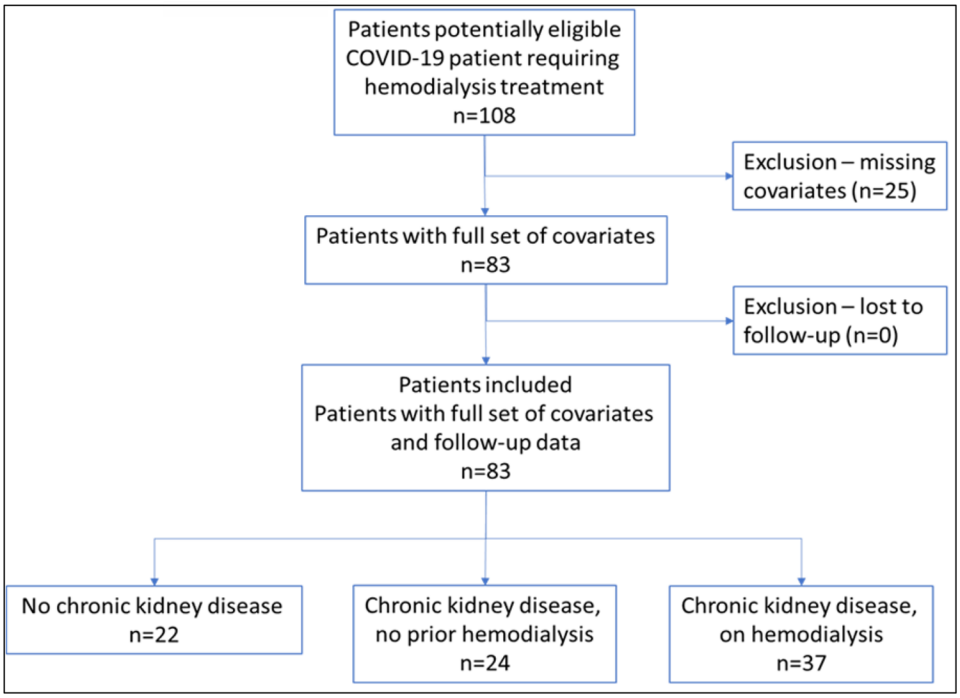

Figure 1. Flow chart of the selection of participants. We included patients admitted to our clinic because of SARS-Cov-2 infection and required hemodialysis treatment. We excluded the patients on PD from our cohort. The missing covariates were almost missing laboratory parameters.

Table 1. Baseline clinical characteristics at the clinical admittance and outcome data of patients requiring hemodialysis during hospitalization for SARS-CoV-2 infection by CKD status.

		nCKD		CKDnonHD		pHD		*p* for	*p* for
	Variable	Mean/median/*n*	SD/IQR/%	Mean/median/*n*	SD/IQR/%	Mean/median/*n*	SD/IQR/%	heterogeneity	trend
	n	22		24		37			
Demographics	Age (years)	61.98	11.34	64.75	12.84	58.52	14.73	0.204	0.34
	Male	17	73.3%	15	62.5%	22	59.5%	0.364	0.186
Medical history	Hypertension	14	63.6%	22	91.7%	34	91.9%	0.008	0.007
	Diabetes mellitus	4	18.2%	17	70.8%	19	51.4%	0.001	0.039
	IHD	0	0.0%	6	25.0%	10	27.0%	0.028	0.017
	Stroke	2	9.1%	4	16.7%	7	18.9%	0.596	0.334
	COPD	1	4.5%	4	16.7%	7	18.9%	0.296	0.149
	CHF	2	9.1%	7	29.2%	9	24.3%	0.223	0.228
Presentation	Dyspnea	19	86.4%	18	75.0%	19	51.4%	0.014	0.004
	O2 saturation*	91	84;95	94	83;97	96	94.98	0.003	<0.001
	Systolic BP (Hgmm)	141	31	142	34	150	31	0.542	0.351
	Diastolic BP (Hgmm)	75	15	76	17	85	20	0.056	0.04
Baseline laboratory values	WBC* (G/L)	8.68	7.08; 14.29	8.03	5.46; 12.65	6.57	3.61; 8.3	0.007	0.002
	Hemoglobin (g/L)	117	25	100	18	99	17	0.003	0.001
	Platelet* (G/L)	195	134; 250	199	181; 287	188	148; 211	0.343	0.414
	CRP (mg/L)	148.43	95.96	140.21	82.89	80.99	69.27	0.003	0.003
	Creatinine (umol/L)	215	227	459	218	656	221	<0.001	<0.001
	Total protein* (g/L)	56.4	52.4; 63.1	59	54.5; 61.6	62.4	58.7; 68.9	0.594	0.313
	Albumin (g/L)	26.9	7.2	28.3	3.7	31.1	7.2	0.044	0.017
Outcomes	Mechanical ventilation	18	81.8%	12	50.0%	3	8.1%	<0.001	<0.001
	ICU	17	77.3%	14	58.3%	5	13.5%	<0.001	<0.001
	Death during follow-up	20	90.9%	23	96.8%	17	45.9%	<0.001	<0.001

BP: blood pressure; IHD: ischemic heart disease; COPD: stroke, chronic obstructive pulmonary disease; CHF: chronic heart failure; ICU: intensive care unit treatment; WBC: white blood count; CRP: C-reactive protein; nCKD: patients with previously normal renal function; CKDnonHD: patients with chronic kidney disease previously not requiring hemodialysis; pHD: patients on regular hemodialysis.

Continuous variables were presented as mean with standard deviation (*SD*) or median with interquartile range (IQR). Categorical variables were presented as numbers (%).

*ANOVA *p* using transformed values, results are given as median IQR.

3.4. Analysis of all-cause mortality

Over a median of 26 (interquartile range 11–266) days of follow-up, 20 of 22 (90.9%) patients without CKD, 23 of 24 (96.8%) CKD patients not on HD treatment, and 17 of 37 (45.9%) of prior HD patients died. Compared to the non-CKD group, the CKD patients not on HD treatment had an increased relative risk of mortality (RR 1.58, 95%CI 0.86–2.92),

Table 2. Baseline clinical characteristics at the clinical admittance and outcome data of patients requiring hemodialysis during hospitalization for SARS-CoV-2 infection by survival status.

		Alive		Deceased		
	Variable	Mean/median/*n*	SD/IQR/%	Mean/median/*n*	SD/IQR/%	*p*
	n	23		60		
Demographics	Age (years)	57.14	15.97	62.81	12.17	0.086
	Male	14	60.9%	40	66.7%	0.618
	Hypertension	21	91.3%	49	81.7%	0.5
Medical history	Diabetes mellitus	9	39.1%	31	51.7%	0.337
	IHD	6	26.1%	10	16.7%	0.36
	Stroke	6	26.1%	7	11.7%	0.173
	COPD	3	13.0%	9	15.0%	1
	CHF	8	34.8%	10	16.7%	0.084
Presentation	Dyspnea	12	52.2%	44	73.3%	0.074
	O2 saturation*	96	94; 98	94	85;96	0.052
	Systolic BP (Hgmm)	153	29	142	33	0.15
	Diastolic BP (Hgmm)	89	19	77	17	0.006
	WBC* (G/L)	6.56	3.8; 8	8.05	5.72; 14.29	0.005
	Hemoglobin (g/L)	106	17	103	22	0.597
	Platelet* (G/L)	186	135; 211	190	156; 264	0.188
Baseline laboratory values	CRP (mg/L)	58.33	55.15	138.09	85.77	<0.001
	Creatinine (umol/L)	663	268	409	259	<0.001
	Total protein* (g/L)	65,3	59.4; 69.5	59	54.2; 62.6	0.116
	Albumin (g/L)	34.7	5.3	27.1	5.7	<0.001
Outcome	Mechanical ventilation	1	4.3%	32	53.3%	<0.001
	ICU	2	8.7%	34	56.7%	<0.001

BP: blood pressure; IHD: ischemic heart disease; COPD: stroke, chronic obstructive pulmonary disease; CHF: chronic heart failure; ICU: intensive care unit; WBC: white blood count; CRP: C-reactive protein.
*Two-sample *t*-tests *p* using transformed values, results are given as median IQR.

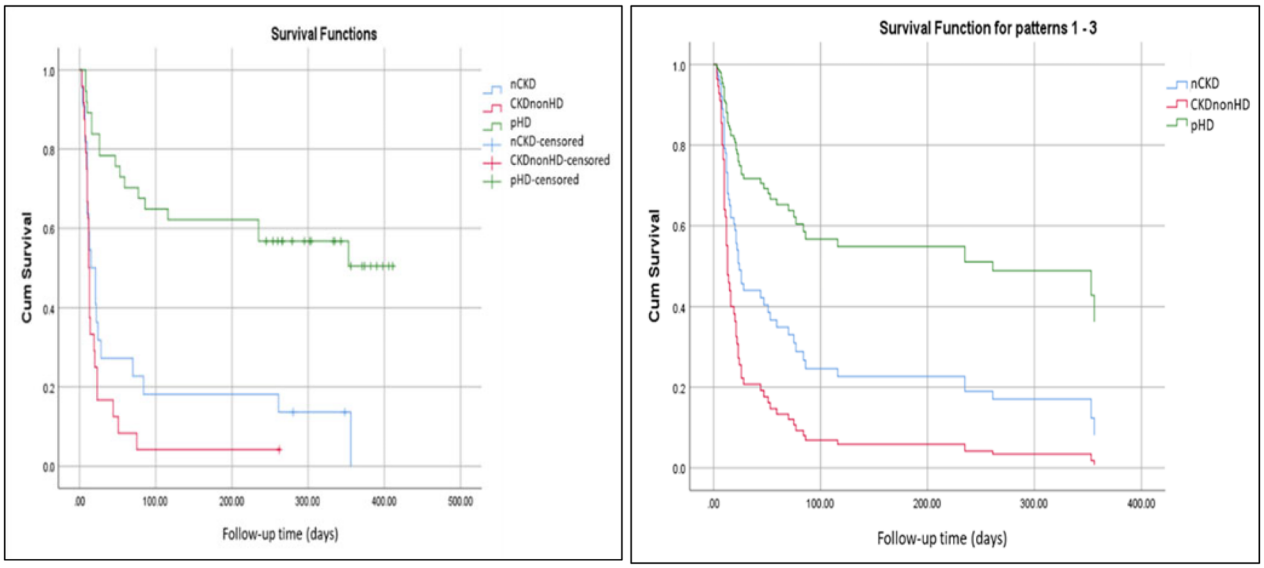

Figure 2. Survival function by CKD status: (A) based on Kaplan–Mayer survival curves and (B) based on Cox models adjusted for serum albumin and C-reactive protein. nCKD: patients with previously normal renal function; CKDnonHD: patients with chronic kidney disease previously not requiring hemodialysis; pHD: patients on regular hemodialysis.

while the chronic HD group had a substantially decreased risk (RR: 0.25, 95%CI 0.13–0.49) (Figure 2(A), Table 3—Model 1).

After further adjustment for the independent predictors of mortality (CRP and albumin) assessed at hospital admission, the relative risk associated with CKD, not on chronic HD, increased to 91% (95%CI 1.02–3.60) and became statistically significant. In contrast, the relative risk associated with prior HD treatment increased but remained significantly lower than that of the non-CKD patients (Table 3—Model 2).

Further adjustment for ICU treatment increased the difference between patients with previously normal renal function and patients with chronic kidney disease previously not requiring hemodialysis. In contrast, the difference between patients with previously normal renal function and CKD patients on regular hemodialysis was attenuated and became non-significant (Figure 2(B), Table 3, Model 3).

Table 3. Hierarchical Cox proportional hazard models with all-cause mortality as an outcome.

	Variable	HR	95% Confidence interval	*p*
Model 1	nCKD	1	(Ref)	
	CKDnonHD	1.581	0.857	2.915
	pHD	0.253	0.131	0.49
Model 2	nCKD	1	(Ref)	
	CKDnonHD	1.913	1.018	3.595
	pHD	0.405	0.202	0.813
	CRP	1.004	1.002	1.007
	Albumin	0.947	0.912	0.983
Model 3	nCKD	1	(Ref)	
	CKDnonHD	2.367	1.224	4.579
	pHD	0.654	0.284	1.509
	CRP	1.003	1	1.007
	Albumin	0.938	0.901	0.977
	ICU treatment	2.024	1.013	4.043

ICU: intensive care unit; CRP: C-reactive protein; nCKD: patients with previously normal renal function; CKDnonHD: patients with chronic kidney disease previously not requiring hemodialysis; pHD: patients on regular hemodialysis.

In Model 1, we compared the three groups, and in Model 2, it was adjusted for CRP and albumin. Model 3 was a further adjustment for the need for ICU treatment.

Other variables available for the model: age, dyspnea, WBC, CRP, creatinine, mechanical ventilation.

4. Discussion

According to the present analysis, patients requiring acute HD during hospitalization due to COVID-19 had >90% all-cause mortality over a median follow-up period of 26 days. In general, patients without CKD had fewer comorbidities and more severe symptoms. In contrast, patients who had previously undergone HD had the least severe symptoms. In a model adjusted for independent predictors of all-cause mortality, CKD patients had almost 100% (95% CI 2–260%), while patients previously on HD had a 60% lower mortality (95% CI 0.20–0.81) than non-CKD patients. After further adjustment for the need for intensive care treatment, the difference in mortality between the non-CKD and prior HD groups became non-significant.

A novel coronavirus leading to coronavirus disease 2019 was first identified in Wuhan, China, in December 2019. By February 2022, over 386 million people had contracted COVID-19 worldwide, of whom almost six million died [15]. The typical clinical spectrum resulting from infection with SARS-CoV-2 is broad, ranging from an asymptomatic response or development of a mild upper respiratory tract infection to a critical illness [16]. Thus, with an increasing patient having a base and being further vaccinated, the SARS-CoV-2 disorder remains a health problem [17–20].

Kidney involvement in patients with COVID-19 is multifactorial and can range from proteinuria and hematuria to acute kidney injury (AKI) requiring hemodialysis. Numerous publications have researched the correlations and risk factors associated with the development of AKI. Hypophosphatemia appears to be an independent risk factor for acute kidney injury [21]. According to the current literature, COVID-19 patients with acute kidney injury have incredibly high mortality rates. Furthermore, it independently predicts all-cause in-hospital death [8]. The kidney involvement after SARS-CoV-2 infection has been extensively published [22–24]. Based on an initial report from Wuhan, the AKI-associated mortality rate is at least 60% at the time of our cohort. Similarly, mortality (70%) has been reported in patients undergoing chronic HD in the US [25,26]. We also found that patients requiring acute HD treatment during COVID-19-related hospitalization had an extremely high mortality rate, accordingly, to published data. Interestingly, our results extend further observations by showing a mortality risk of >90% over an extended follow-up period (Figure 2).

Among the groups in the present study, we found the highest mortality in patients with CKD requiring acute HD during hospitalization, where almost all patients died. This is a staggering result because patients in the non-CKD group had a more severe presentation, with significantly more frequent complaints of dyspnea at admission and more frequent mechanical ventilation and intensive care requirements.

Mortality in our cohort was associated with the severity of COVID-19, with significantly higher CRP and WBC values among patients who died. Several studies have documented an association between COVID-19 severity and circulating levels of CRP and interleukin-6 [27]. Hypoalbuminemia at clinical admittance is common among COVID-19 patients and is closely related to inflammatory markers and clinical outcomes. Hypoalbuminemia is strongly associated with respiratory impairment, disease severity, and inflammatory state [28]. According to a clinical study, it was discovered that acid-base imbalances were present in a majority of COVID-19 patients upon admission. The most prevalent alterations observed were metabolic and respiratory alkalosis [29]. Although arterial blood gas analysis was typically a routine examination, not all data was recorded due to isolation regulations and the many patients treated. Therefore, this data was not used in the statistical analyses.

Before the vaccination era—in contrast to our findings—a few studies have reported an extremely severe course and poor prognosis in patients on hemodialysis with COVID-19. For example, compared with the expected 1.2% mortality in matched controls on dialysis without COVID-19, COVID-19 patients on hemodialysis had an absolute mortality of over 20% and a relative risk of 21 [95% confidence interval (CI) 18.6–23.9] [30–32]. In addition, a large cohort of over 80,000 participants demonstrated positive associations between social deprivation and the risk of COVID-19 and almost all chronic health conditions, including hemodialysis [33]. But not only the patients on hemodialysis and those with kidney transplantation also have significantly higher mortality than those without kidney disease [34]. Other authors also described exceptionally high mortality concerning the second wave among patients treated for HD [35]. It should be noted here, however, that the results of these studies only examined hospital mortality and did not follow the outcome of discharged patients.

Many end-stage renal disease (ESRD) patients undergo peritoneal dialysis (PD). Cohorts from China found a similar incidence of symptomatic COVID-19 among patients with PD

to that of the general population, indicating that the PD population was not at high risk for COVID-19. Multiple and severe comorbidities, but not the infection itself, may contribute to prolonged hospitalization and increased mortality in patients with PD [36]. The overall mortality (8.5%) of PD patients between 1 January 2020 and 12 April 2020, increased compared with the mortality (5.7%) of the corresponding period in 2019. Two systematic reviews reported comparable mortality rates between critically ill patients with AKI undergoing PD and extracorporeal dialysis [37]. Based on this, acute PD might be a suitable treatment option for COVID-19-related AKI [38,39]. In our cohort, we did not enroll patients on PD.

The surprisingly low mortality of our patients with previous HD treatment and SARS-CoV-2 infection could be partially explained by the fact that an important indication for the hospitalization of patients with chronic HD was the isolation of these patients and the prevention of transmission during transport to the dialysis unit. This finding supports that the patients in the pHD group had the least severe presentation at admission. Complete isolation of HD patients with COVID-19 is a general clinical practice worldwide [40].

Although isolation most likely played a vital role in the lower risk of death in patients undergoing chronic HD, nearly half of these patients died during the extended follow-up period. Mortality reported in other patient groups suggests that in addition to the effect of acute COVID-19 and its immediate complications, severe complications and consequent deaths can be expected months after hospitalization. These factors will likely affect the high overall mortality of non-CKD and non-dialysis CKD patients. Although fewer patients in the CKD group who were not previously on HD required intensive care, the in-hospital and overall mortality rates were the highest in this group. Our study's findings are consistent with a recently published paper that showed no connection between COVID-19 infection and higher death rates among patients with end-stage renal failure [41].

Another hypothesis of our findings is that anti-inflammatory factors, e.g., erythropoietin and sodium-heparin, contributed to these results. Erythropoietin (EPO) is a hormone/cytokine produced mainly by the kidneys *via* hypoxia-inducible factor-2 as its primary transcription factor. However, EPO has other beneficial cytoprotective effects [42]. The protective effects of EPO were attributed to its impact in inhibiting the expression of nuclear factor-κB (NF-κB) in lung tissues, inhibition of interleukin-6 (IL-6), and tumor necrosis factor-alpha as proinflammatory cytokines and improvement of anti-inflammatory cytokine IL-10 levels [43]. Increased interleukins (e.g., IL-1β and IL-6) are independently associated with disease severity/mortality, and therapies targeting IL-1β and IL-6 effects show promising results. Theoretical the EPO immunoregulating effects include inhibiting IL-1β and IL-6 production by monocytes and promoting regulatory T-cell survival [44]. During hemodialysis, it is necessary to perform anticoagulation of the dialysis circuit to avoid blood clotting in the system due to Factor VII, platelet, and leukocyte activation. Anticoagulation is usually performed utilizing heparin or a low-molecular-weight form [45]. Heparin comprises a heterogeneous mixture of sulfomucopolysaccharides and a minimum peptide component of two amino acids (glycine and serine). Heparin exerts a binding capacity to the endothelial surface and various plasma proteins. The unfractionated heparin (UFH) molecular weight range is 5000–30,000. Low-molecular-weight heparin (LMWH) fractions effectively inhibit the activated factor X (factor Xa) while exerting a less inhibitory effect on thrombin compared to the unfractionated forms [46]. LMWH has some antiviral properties *in vitro*, and it is routinely used in COVID-19 patients to prevent or circumvent the activation of the coagulation cascade induced by inflammation. In a retrospective study, LMWH therapy reduced interleukin-6 release and activity, which is responsible for the 'cytokine storm', and treated patients also had a higher percentage of lymphocytes [47]. Anti-coagulation may constitute a promising tool for treating SARS-CoV-2, reducing the cytokine storm and the risk for thrombotic complications [48]. Therefore, it is possible that hemodialysis patients could be protected from COVID-19 virus infection by the LMWH used in every hemodialysis session [49].

It must be emphasized that individuals with HD exhibit notable long-term humoral and cellular immune responses following natural infection with COVID-19, unlike non-kidney adults. It appears that patients with HD who have recovered from COVID-19 naturally do not need any changes made to their vaccination program. This means they do not require higher doses or additional vaccine shots, as is often recommended for hepatitis B immunization [50].

4.1. Strengths and limitations

Our study has some strengths that have to be mentioned. Most participants were also included in the prospective data collection, and more details were collected with better precision than expected in usual clinical care. Furthermore, the follow-up period did not end with the emission of patients; therefore, mortality follow-up was at least six months for each participant (although, given the high mortality, the mean and median were much shorter). Our study had the most extended overall follow-up period among patients on HD with COVID-19. Previous reports were limited to hospital deaths, but we diligently tracked and analyzed our patients and study groups beyond their discharge. To the best of our knowledge, this is the single longest follow-up study. It should also be noted that we could track the mortality data for all included participants.

However, this study has some limitations. First, the number of participants was small, and we presented only one clinic experience, which limited the statistical power. Therefore, we had to limit the number of covariates in the multivariate models, and given the wide confidence intervals, the magnitudes of the effect sizes could not be judged well. Our analysis of chronic HD patients is limited by selection bias related to the fact that the indication for hospitalization was not always the severity of the disease but the need for

isolation. Given the sudden onset of the COVID-19 epidemic and the significant strain on the healthcare system, we excluded many potential participants because of missing covariates. Furthermore, as intensive care admission was not decided at the time of entry for all cases, its use in the final model could lead to over-adjustment. However, the requirement for intensive care is strongly related to disease severity.

5. Conclusions

Patients requiring acute hemodialysis during hospitalization for COVID-19 had a remarkably high all-cause mortality rate, as known from the literature since the outbreak of COVID-19 infection worldwide. In our long follow-up cohort, CKD patients not previously requiring hemodialysis fared worse than those without known CKD before hospitalization. In the background of the obtained results, several hypotheses can be put forward; the much better survival of chronic hemodialysis patients with long-term follow-up suggests the role of unmeasured confounding or selection bias related to the hospitalization of asymptomatic patients in preventing the spread of the disease during transport to treatment. Chronic hemodialysis creates a special milieu, which can have both advantages and disadvantages. The evidence we have gathered suggests that implementing measures to avert acute kidney injury in individuals with COVID-19 has the potential to lower the fatality rate associated with the disease.

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None.

Ethical approval

All study-related procedures were performed by the 1964 Declaration of Helsinki's ethical standards and later amendments. Local ethical permission was obtained from the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (registration number SE-RKEB 245-1/2020). The Hungarian laws of the ethics committee waived the need for informed consent, as no specific study-related procedures were performed.

Informed consent

Enrolled patients signed the informed consent form and agreed to participate in the study and publish the results in an online open-access journal. Our manuscript contains no identifying information or images of patients. However, this consent form was not applicable. Therefore, only aggregate data were used, and no identifiable patient data were revealed.

Author contributions

ÁGP designed the study and coordinated its execution. ÁGP and ÁGT wrote the first version of the manuscript. PK, MJ, and ÁK collected data. ÁGT and NL performed statistical analyses. All authors critically revised the manuscript. IT oversaw and coordinated study and manuscript preparation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to intellectual property but from the corresponding author upon reasonable request.

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