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ORIGINAL PAPER

Hemodialysis dose and long-term COVID-19 outcomes – a retrospective cohort study

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ABSTRACT

Introduction and aim. Long-term outcomes of COVID-19 pose a global challenge, particularly impacting individuals with underlying health conditions, including those who have undergone hemodialysis (HD). The study aimed to investigate the relationship between preexisting dialysis dose, measured by single pool Kt/V (spKt/V), and long-term outcomes of COVID-19 in patients undergoing HD.

Material and methods. Demographic, clinical, and laboratory parameters following COVID-19 recovery, and long-term outcomes, including the presence of COVID-19 sequelae, hospitalization, and all-cause mortality during a year after COVID-19 were retrospectively analyzed.

Results. Out of the 195 patients included, there were 108 males (55.4%) and 87 females (44.6%), with a median age of 56 (44-63) years and a dialysis duration of 49 (31.3–85.2) months. Patients with spKt/V<1.4 had a significantly increased risk of long-term COVID-19 sequelae (HR 9.1, 95% CI: 3.4; 24.6), hospitalization (HR 7.6, 95% CI: 3.9; 14.6), and all-cause mortality (HR 8.5, 95% CI: 2.9; 25.8) within one year after COVID-19 recovery compared with those with spKt/V≥1.4. spKt/V cutoff point of ≤1.3 emerged as a significant risk factor for one-year hospitalization and mortality within our cohort.

Conclusion. Suboptimal dialysis dose, as indicated by spKt/V < 1.4, is associated with adverse long-term COVID-19 outcomes in patients undergoing HD. Optimizing dialysis adequacy may mitigate these risks. Further research is needed to validate these findings and explore interventions to improve outcomes in this vulnerable population.

Keywords. dialysis dose, hemodialysis, hospitalization, long COVID, mortality

Introduction

The COVID-19 pandemic has left an indelible mark on global healthcare systems, with millions of individuals affected by the severe acute respiratory syndrome caused by the novel coronavirus (SARS-CoV-2).[1] While much attention has been rightfully directed towards preventing the spread of the virus and treating acute cases, an emerging concern lies in the long-term health consequences experienced by survivors of COVID-19, particularly those with pre-existing chronic kidney disease (CKD) who require hemodialysis (HD).[2,3]

Patients undergoing HD are at higher risk of contracting COVID-19 and related complications due to multifactorial risks, including underlying comorbidities, immunosuppression, and frequent dialysis facility visits, which contribute to their increased vulnerability.[2–4] Vaccination against SARS-CoV-2 has been found

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to be highly effective in preventing severe illness, hospitalization, and death in the HD population.[5,6] However, recent studies have suggested that even fully vaccinated individuals, including patients undergoing HD, may still develop long-term COVID, a condition characterized by persistent symptoms that extend beyond the acute phase of COVID-19.[6,7]

Long-term COVID presents a wide range of symptoms that vary in severity and persist for extended periods, spanning weeks, months, or even years.[3,8] Ongoing research is diligently investigating the trajectory of long-term COVID, yet the precise mechanism remains generally unknown.[9,10] Potential factors being explored include the activation of autoimmune antibodies, reactivation of latent viruses, the persistence of SARS-CoV-2 in other organs, and direct organ damage resulting from chronic immune dysregulation.[10] Consequently, there is a current hypothesis that chronic pre-infection inflammation could be a potential contributor to the development of long-term COVID.[9,10]

The measurement of single-pool Kt/V (spKt/V) is a standard practice in clinical settings to gauge dialysis adequacy and is integral in determining the overall health and clinical outcomes of patients receiving HD treatment.[11,12] Specifically, for patients on a thrice-weekly HD regimen, it is recommended to achieve a target spKt/V of 1.4 per HD session, with a minimum delivered spKt/V of 1.2.[13] However, realizing this goal is not always feasible due to various factors, including vascular access issues, individual patient variability, comorbidity burden, and practical constraints.[11] Falling below the recommended spKt/V of 1.2 has been associated with persistent chronic inflammation and increased oxidative stress, factors that may potentially amplify the inflammatory response triggered by a COVID-19 infection.[14,15] This, in turn, could contribute to the emergence of long-term COVID symptoms in patients undergoing HD.

Despite the implications of suboptimal HD doses, a comprehensive examination of the relationship between HD dose and long-term COVID-19 outcomes has been lacking.

Aim

To address this knowledge gap, we conducted a retrospective cohort study investigating the impact of HD doses on long-term COVID-19 outcomes. Our hypothesis posited that reduced HD doses would be associated with worse long-term COVID-19 outcomes in patients receiving maintenance HD. To test this hypothesis, we assessed the relationship between pre-existing spKt/V and 1-year COVID-19 clinical outcomes, including the presence of long COVID sequelae, hospitalization following recovery from COVID-19, and all-cause mortality.

Material and methods

Study design and setting

This retrospective cohort study was conducted in collaboration between two dialysis centers: Dialysis Medical Center LLC "Link-Medital" in Odesa, Ukraine, and Dialysis Medical Center LLC "Nephrocenter" in Kyiv, Ukraine, in the scientific partnership with the State Institution "Institute of Nephrology of the National Academy of Medical Sciences of Ukraine," also located in Kyiv, Ukraine. The study was carried out as a part of the Institute's ongoing project titled "Exploring the Mechanisms of Development and Identifying Therapeutic Targets for Post-COVID Syndrome in Dialysis Patients," which is registered under the National Study Registration Number 0122U000144. The study adhered to the principles outlined in the Declaration of Helsinki and took place from May 2021 to May 2023. The study protocol received approval from the Institute Ethics Committee (protocol number: 2-2021, dated April 6, 2021).

Study participants

The study included individuals aged 18 and above who had undergone HD for a minimum of three months before acquiring COVID-19. The confirmation of COVID-19 diagnosis involved either the detection of SARS-CoV-2 RNA through real-time reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab specimens or the observation of imaging results consistent with COVID-19. Excluded from the study were patients who were younger than 18, had a dialysis duration of less than three months before their COVID-19 diagnosis, had been hospitalized in the three months leading up to the study, received kidney transplants during the study period, were undergoing immunosuppressive therapy, had systemic or malignant diseases, or were currently experiencing acute inflammatory conditions.

All the patients were dialyzed three times a week for 4 hours using Fresenius 5008S High Volume HDF System. The HD procedure involved the use of bicarbonate-based dialysate, volumetric ultrafiltration control, and single-use synthetic (polysulfone) dialyzers. The median blood flow rate was 300 mL/min, and the dialysate flow rate was 500 mL/min. Heparin was administered as the standard anticoagulant.

Data collection

We collected a comprehensive dataset from eligible participants, covering various facets including demographic information, a three-month average of pre-existing spKt/V values, and crucial clinical and laboratory indicators. spKt/V was measured using the second generation ln formula:

$$spKt/V = -\ln(R - 0.008 \cdot T) + \\ + (4 - 3.5R) \cdot Weight\ loss/V,$$

where 'R' is the ratio of post-dialysis to pre-dialysis blood urea; 'V' is total body water volume; 'T' is dialysis session time, or treatment time in hours; 'ln' represents the natural logarithm with a base of 'e,' where 'e' has a value of approximately 2.718.[12,16]

The collected indicators included body mass index (BMI), anuria status, comorbidities (such as diabetes mellitus, hypertension, and a history of cardiovascular disease), the type of vascular access used for dialysis, hemoglobin levels, platelet counts, D-dimer, serum electrolyte concentrations, C-reactive protein (CRP) levels, intact parathyroid hormone levels (iPTH), ferritin, albumin, and cholesterol levels. The results of the first laboratory investigation conducted following COVID-19 recovery were utilized for all the data. This investigation took place at a median of 32 (28–37) days after the onset of COVID-19.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Anuria was defined as daily diuresis of less than 100 mL. The measurement of data involved the use of an automatic analyzer "Flexor Junior" (Vital Scientific, Netherlands) for biochemical measurements, and hematological parameters of blood were determined using an "ABX Micros-60" (Horiba Medical, France). iPTH levels were assessed through an immunoradiometric assay, and electrolyte levels were measured using standard autoanalyzer techniques.

In addition, we meticulously documented the details of COVID-19 infections, capturing specific information such as the date of infection onset, the vaccination status before contracting COVID-19, radiologic findings (the percentage of lung damage on computed tomography [CT] images), the necessity of oxygen therapy during the acute phase of the disease, the presence of long-term COVID-19 sequelae, any cases of hospitalization following COVID-19 recovery, and instances of mortality. The identification of long-term COVID sequelae involved a meticulous review of medical records, focusing on whether patients self-reported post-COVID symptoms or if documented medical conditions could explain these symptoms.

Outcome measures and their definitions

The primary outcome measures included:

The presence of long-term COVID sequelae

Long-term COVID sequelae encompassed a range of persistent symptoms and health issues that linger beyond the acute phase of COVID-19. They included but were not limited to respiratory, neurological, cardiovascular, or other medical conditions arising as a result of the initial COVID-19 infection and could not be explained by alternative diagnoses.

The incidence of hospitalization following recovery from COVID-19

This outcome referred to instances where participants required hospitalization for medical treatment or care after their recovery from COVID-19 infection. It aimed to assess the need for hospital-based medical intervention following the resolution of the initial COVID-19 illness.

The rate of all-cause mortality within one year following COVID-19 infection

This measure entailed recording the number of deaths due to any cause among the study participants within a year after contracting COVID-19.

Statistical analysis

All statistical analyses and graphs were performed using the MedCalc Statistical Software version 22.007 (MedCalc Software Ltd, Ostend, Belgium). Continuous variables were presented as medians (M) with interquartile ranges (Q25-Q75) due to non-normal distribution. Categorical variables were expressed as counts and percentages. To assess the differences between groups based on dialysis dose (spKt/V<1.4 vs. spKt/V≥1.4), we employed the chi-squared (χ^2) test for categorical variables and independent t-tests or Mann-Whitney U tests for continuous variables, as appropriate. Correlation analysis was done using the Pearson test. We employed Kaplan-Meier survival curves to assess the one-year survival probability of patients in relation to dialysis dose. Log-rank tests were conducted to determine the statistical significance of differences between the two dialysis dose groups. A multivariate Cox proportional hazards regression model was used for the primary outcomes of interest (long-term COVID-19 sequelae, one-year hospitalization, and all-cause mortality). We calculated hazard ratios (HR) with 95% confidence intervals (CI) to evaluate the associations between dialysis dose and these outcomes. In the analyses, we adjusted for potential confounders, including patient age, dialysis vintage, diabetes status, a history of cardiovascular disease and vaccination, and the requirement of oxygen support during the acute phase of COVID-19. To evaluate the predictive ability of spKt/V values for COVID-19 outcomes, we performed a Receiver Operating Characteristic (ROC) analysis. We assessed the area under the curve (AUC) and determined optimal cutoff values to maximize sensitivity and specificity for predicting the outcomes.

Results

Patient presentation and initial COVID-19 outcomes

Out of the initial cohort of 246 eligible patients who survived the acute phase of COVID-19, we excluded 51 patients due to them meeting exclusion criteria (Fig. 1).

Consequently, our study comprised 195 patients, with a median dialysis vintage of 49 (31.3–85.2) months. The average age of the study population was 56 (44–63)

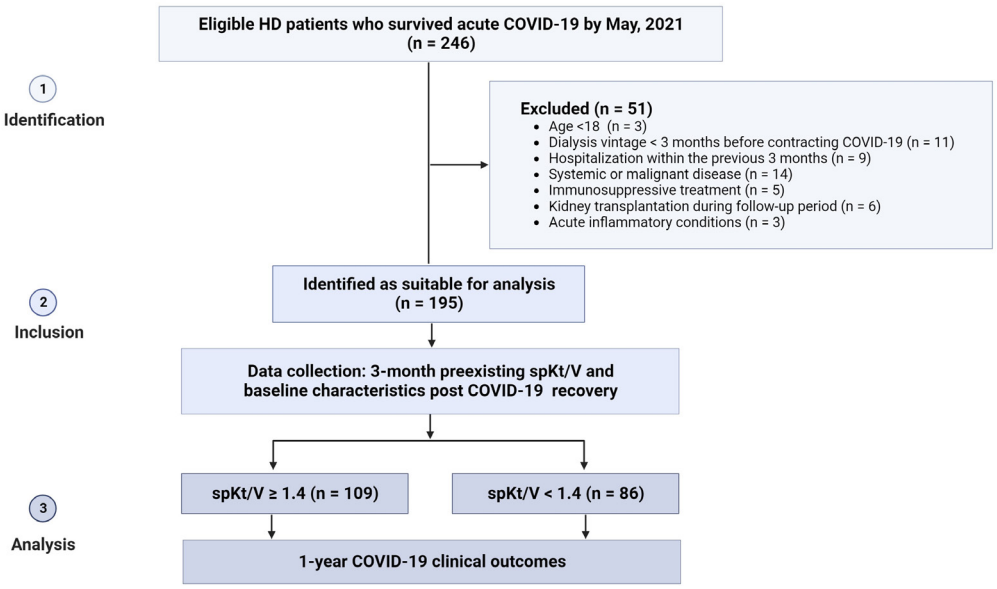

Fig. 1. The study flowchart

years, with 108 males, accounting for 55.4% of the cohort. The most prevalent comorbidities among the participants were hypertension, affecting 189 (97%) of them, followed by obesity (BMI ≥ 30 kg/m^2) in 41 (21%), cardiovascular disease in 31 (15.9%), and diabetes in 26 (13.3%).

During the acute phase of COVID-19, the most commonly reported symptoms were fever (131/67.2% of patients), cough (115/59%), and fatigue (103/52.8%). Interestingly, 24 (12.3%) of patients remained asymptomatic. Additionally, 77 (39.5%) of the patients underwent lung CT scans, and only 4 (5.2%) of them exhibited significant pulmonary damage of ≥50%. Nevertheless, 38 (19.5%) of the patients required hospitalization with supplemental oxygen.

Notably, 25 (12.8%) of the patients had received full vaccination against COVID-19 using either the Pfizer-BNT-162b2 or Moderna-mRNA-1273 vaccine before contracting the virus.

The 3-month average dialysis dose before the onset of COVID-19 infection exhibited a range from 1.1 to 2, with a median spKt/V value of 1.4 (1.3–1.5). Notably, 109 patients (55.9%) had spKt/V levels exceeding 1.4, while 84 patients (43.1%) fell within the range of spKt/V values between ≥1.2 and < 1.4; and only a small fraction, consisting of 2 patients (1.02%), fell below the target level of spKt/V (<1.2), primarily due to issues related to inadequate vascular access.

To further analysis, we categorized patients based on their attainment of the target spKt/V value. As demonstrated in Table 1, patients with spKt/V <1.4 displayed higher blood pressure, CRP, BMI, and D-Dimer levels in comparison to patients with spKt/V ≥1.4.

Expectedly, they exhibited lower levels of Hb and calcium. In addition, this group showed a higher preva-

Table 1. Characteristics of the study cohort stratified by 3-month average dialysis dose preceding COVID-19 infection*

	Patients with spKt/V ≥ 1.4 (n=109)	Patients with spKt/V < 1.4 (n=86)	p
Demographic and routine clinical data			
Male gender, n (%)	57 (52.3%)	51 (59.3%)	0.33
Age, years	56 (46–62)	56 (42.5–64)	0.87
Dialysis vintage, months	45.5 (29–103.5)	49 (36.5–66)	0.91
Temporary vascular access, n (%)	2 (1.83%)	5 (5.82%)	0.14
Hypertension, n (%)	104 (95.4%)	85 (98.8%)	0.12
Systolic blood pressure, mm Hg	140 (120–145)	140 (130–150)	0.02
Diastolic blood pressure, mm Hg	75 (71.3–80)	80 (75–90)	0.04
Diabetes mellitus, n (%)	9 (8.2%)	17 (19.7%)	0.02
Cardiovascular disease, n (%)	12 (11.1%)	19 (22.1%)	0.03
BMI, kg/m^2	24.2 (21.8–27.5)	28.6 (23.8–31.5)	<0.0001
spKt/V	1.45 (1.4–1.56)	1.3 (1.22–1.36)	<0.0001
Hb, g/L	105 (94.5–115)	98 (85.2–112)	0.007
Serum albumin, g/L	38.5 (36.1–41.6)	36.7 (35.5–40.7)	0.12
Calcium, mmol/L	2.26 (2.16–2.35)	2.19 (2.02–2.29)	0.03
Phosphorus, mmol/L	1.58 (1.29–1.96)	1.72 (1.48–2.02)	0.08
iPTH, ng/L	307.0 (129.3–587.5)	224.0 (126.0–557.9)	0.49
Total cholesterol, mmol/L	4.9 (3.6–5.6)	4.6 (3.8–5.3)	0.63
CRP, mg/L	10.2 (4.1–16.9)	12.7 (6.9–18.8)	0.04
Ferritin (ng/mL)	301 (159.3–476.5)	322 (235.5–401)	0.21
Platelet count (/mm^3)	214.0 (172.2–248.2)	202.0 (182–224)	0.31
D-Dimer (ng/mL)	420 (263–890.7)	522 (257.5–906.3)	0.03
Initial COVID-19 outcomes			
Vaccinated status for COVID-19, n (%)	16 (14.7%)	9 (10.5%)	0.38
Area of lung lesions on CT images, %	15 (11.3–30)	25 (15–40)	0.02
Hospitalization with oxygen supply, n (%)	14 (12.8%)	24 (27.9%)	0.008

* BMI – body mass index, CRP – C-reactive protein, CT – computed tomography, Hb – hemoglobin, iPTH – intact parathyroid hormone, spKt/V – single-pool Kt/V

lence of obesity, diabetes, and a history of cardiovascular disease. They also presented a more extensive degree of pulmonary damage and a higher rate of hospitalization requiring oxygen support during the acute phase of COVID-19. Notably, there was an inverse correlation observed between the extent of pulmonary damage on CT scans and the patients' preexisting spKt/V, as illustrated in Fig. 2.

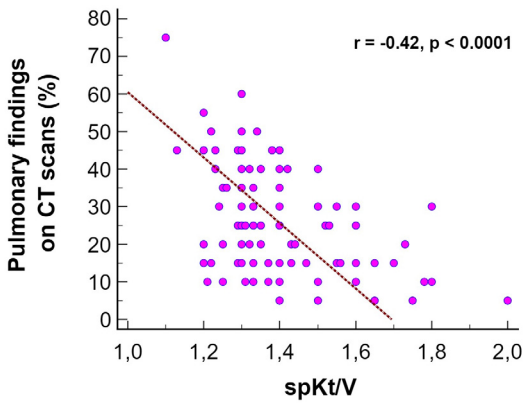

Fig. 2. Correlation between the percentage of COVID-19-associated pulmonary involvement and preexisting spKt/V in patients undergoing HD

Preexisting spKt/V and long-term COVID-19 outcomes

Over the one-year follow-up period, long-term COVID-19 sequelae manifested in 146 patients, accounting for 74.8% of the cohort. Additionally, 37 (18.9%) patients required hospitalization, and 13 patients (6.7%) died. Among those hospitalized during the long-term COVID period, cardiovascular events were the leading cause, responsible for 14 (38.8%) cases, followed by infections in 11 (29.7%) cases, and gastrointestinal bleeding in 4 cases (10.8%). Cardiovascular events accounted for 5 (38.5%) cases of death, sepsis for 4 (30.7%) cases, stroke for 2 (15.4%) cases, pulmonary embolism for 1 (7.7%) case, and 1 (7.7%) case remained classified as unknown.

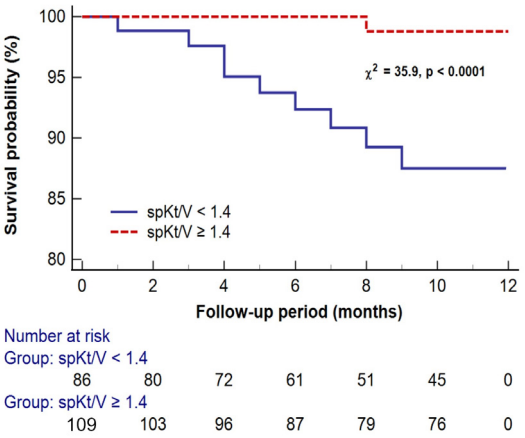

Fig. 3. Survival probability of patients undergoing HD one year after COVID-19, stratified by attainment of the target spKt/V level prior to infection

Patients with spKt/V levels below 1.4 exhibited a notably higher prevalence of long-term COVID-19 sequelae (χ^2 = 50.2, p < 0.0001), hospitalization rate (χ^2 = 36.7, p < 0.0001), and mortality (χ^2 = 12.8, p = 0.003) when contrasted with those having spKt/V values of 1.4 or greater. The Kaplan-Meier analysis revealed a significantly higher one-year survival probability following COVID-19 in patients with spKt/V ≥1.4 (Fig. 3).

In the multivariate Cox-regression analysis, adjusted for patient age, dialysis vintage, diabetes, a history of cardiovascular disease, vaccination status, and severe acute-phase COVID-19 (defined as the need for oxygen support), preexisting spKt/V <1.4 was associated with a 9-fold higher risk of experiencing long-term COVID-19 sequelae (HR 9.1, 95% CI: 3.4; 24.6), a 7-fold increase in the likelihood of hospitalization within one year following COVID-19 (HR 7.6, 95%

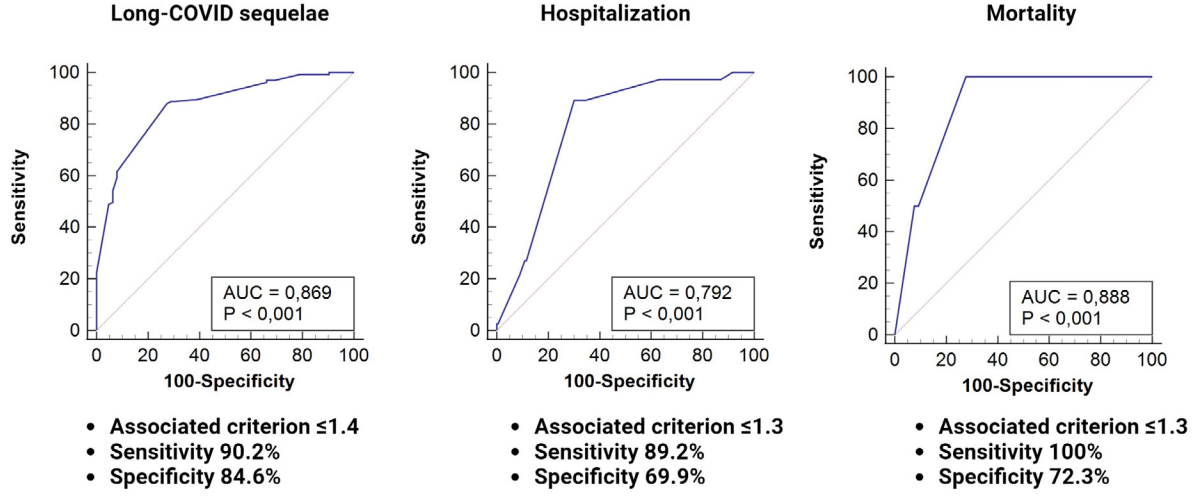

Fig. 4. ROC analysis for COVID-19 outcome prediction using spKt/V value in patients undergoing HD

CI: 3.9; 14.6), and an 8-fold rise in mortality risk (HR 8.5, 95% CI: 2.9; 25.8).

The ROC analysis was employed to discern the predictive accuracy of specific spKt/V cut-off points in relation to long-term COVID-19 outcomes. The findings of this analysis revealed that for the anticipation of the long-COVID syndrome, a spKt/V cut-off point of less than 1.4 demonstrated notable sensitivity and specificity. However, when it came to predicting long-term hospitalization and one-year mortality among patients undergoing HD, the ROC analysis indicated that a spKt/V cut-off point ≤1.3 exhibited superior predictive performance (Fig. 4).

Discussion

The present study sought to elucidate the intricate relationship between preexisting dialysis dose, as indicated by spKt/V values, and the long-term outcomes of COVID-19 in the cohort of patients treated with HD. Our hypothesis stems from recognizing that dialysis adequacy encompasses a multifaceted array of factors extending beyond urea removal alone. It involves considerations such as the quality of vascular access, the presence of comorbidities, fluid balance management, correction of malnutrition, acidosis, and anemia, maintenance of electrolyte homeostasis, and addressing chronic inflammation.[17–20] Within this context, a reduced dialysis dose can be seen as a reflection of this intricate interplay of factors, potentially contributing to unfavorable COVID-19 outcomes in patients undergoing HD. However, to the best of our knowledge, only two studies have delved into the relationship between dialysis dose and COVID-19.[21,22] Kooman et al. illustrated that deviating from target dialysis doses is a potential risk factor for 30-day COVID-19-related mortality in the HD population.[21] The second study has recently explored whether differences exist in dialysis adequacy between HD patients with COVID-19 and those without infection.[22] Nevertheless, neither of these reports has furnished evidence of a long-term association between dialysis dose and COVID-19 outcomes, including the specific Kt/V values as predictors.

In line with the aforementioned studies, our findings underscore the critical importance of optimizing dialysis doses to mitigate both immediate and long-term adverse outcomes in COVID-19 patients.[21,22] We found an inverse relationship between spKt/V values and the extent of pulmonary damage observed on CT scans. Furthermore, patients with preexisting spKt/V values below 1.4 were at a heightened risk of developing long-term COVID-19 sequelae, experiencing extended hospitalization during a year after COVID-19 recovery, and facing an increased risk of all-cause mortality when compared to patients receiving spKt/V≥1.4. Our data specifically indicated that a spKt/V cutoff point of ≤1.3 emerged as a significant risk factor for one-year hospitalization and mortality within our cohort.

The evaluation of dialysis adequacy through spKt/V urea is a widely utilized method to assess the administered dialysis dosage.[23] Although acknowledged for its limitations, it is recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines as a meaningful metric for evaluating the impact of dialysis on patient survival.[13,24] According to these guidelines, patients receiving HD three times a week should aim for a target spKt/V of 1.4 per session, with a minimally acceptable delivered dose set at spKt/V of 1.2. In our patient cohort, the majority (55.9%) achieved spKt/V values of 1.4 or higher, while 43.1% received at least the minimal dose (spKt/V >1.2 and <1.4), and merely 1% fell below the minimal dialysis threshold (spKt/V < 1.2). Consequently, it may be reasonably inferred that the adequacy of dialysis should not have a significant influence on COVID-19 outcomes within our cohort. However, exceeding the recommended dialysis dose has been associated with reduced mortality rates and decreased risk of hospitalization.[25] Hence, achieving the target or surpassing the minimal dose requirement might hold the potential to mitigate the risks of COVID-19-associated hospitalization and mortality, as demonstrated in our study.

The association of suboptimal or reduced dialysis dose with increased risk of long-term COVID-19 outcomes can be explained by a convergence of factors. First, patients undergoing HD typically present with compromised immune systems, as even a single hemodialysis session can contribute to immune deficiency.[26–28] This susceptibility renders them more severe COVID-19 and more unfavorable long-term clinical outcomes compared to the general population.[29,30] Insufficient dialytic efficacy further weakens this already compromised immune response, potentially exacerbating the severity of the infection. While the long-term consequences of COVID-19 in the HD population are not yet fully understood, studies have shown that COVID-19 can involve persistent sequelae and other clinical complications that persist for weeks to months after initial recovery.[3,8] Moreover, recent evidence has shown that the adequacy of HD can independently predict seroconversion in patients receiving HD following anti-COVID vaccination.[31] This highlights the potentially far-reaching impact of dialysis adequacy, extending its implications beyond immediate COVID-19 outcomes.

Our findings revealed an increased risk of one-year hospitalization and mortality in patients with preexisting spKt/V <1.4, regardless of factors such as patient age, dialysis vintage, diabetes, history of cardiovascular disease, vaccination status, and severe acute-phase COVID-19. Although there is limited description of long-term COVID-19-associated mortality in patients

treated with HD, existing studies provide some insights. For instance, Och et al. have reported a mortality rate of 37.4% and 39.3% at 3 and 6 months, respectively, in their longitudinal cohort study.[8] Another prospective study found a 35.7% mortality rate over 12 months among 56 HD patients with COVID-19.[32] These studies indicate that elevated mortality rates in COVID-19 patients on HD extend beyond the initial hospitalization, persisting into the first year after diagnosis. In our study cohort, the mortality rate was notably low (6.7%), considering the generally high dialysis adequacy. It's important to note that direct comparison with the mentioned studies is challenging due to the absence of Kt/V data in their reports. Given the intricate interplay of long COVID, comorbidities, and cardiovascular and all-cause mortality in HD patients, establishing a specific timeframe after COVID-19 infection when mortality can be solely attributed to long COVID is challenging. The multifactorial nature of mortality in this population requires a comprehensive assessment of individual patient characteristics, encompassing the presence of long COVID symptoms, the severity of comorbidities, and the impact of persistent inflammation.

Second, reduced spKt/V has been shown to be associated with toxins accumulation and potentially indicates the systemic inflammatory stress determined by increased CRP levels, up-regulation of proinflammatory cytokines and chemokines, and downregulation of anti-inflammatory cytokines.[14,20,27] Chronic inflammation is a well-documented characteristic in patients on HD, often stemming from various factors like the accumulation of uremic toxins, oxidative stress, and constant exposure to dialysis membranes, among others.[33] Intriguingly, in the context of COVID-19, chronic inflammation at baseline may have a somewhat paradoxical effect, potentially offering a degree of protection against severe outcomes in patients undergoing HD.[34] However, this amplified immune response can be a double-edged sword. On the one hand, it might help combat the virus more effectively. On the other hand, it can lead to an excessive and dysregulated inflammatory response, known as a "cytokine storm," which is associated with severe lung damage and complications seen in severe cases of COVID-19.[35] Our finding of an inverse association between spKt/V values and pulmonary damage observed on CT scans indirectly supports this hypothesis. Suboptimal or reduced dialysis dose, indicating insufficient toxin removal, contributes to the systemic inflammatory state observed in HD patients, heightening susceptibility to severe lung injury upon COVID-19 infection. This aligns with previous research suggesting that uremic toxin indoxyl sulfate plays a toxicophysiological role as a mediator in the kidney-lung axis.[36] Moreover, our previous report demonstrated that increased preexisting serum indoxyl sulfate was associated with poor COVID-19 outcomes in HD patients, including the severity of pulmonary damage observed on CT scans.[4] Although our study did not directly measure cytokine levels due to its retrospective nature, a notable increase in CRP levels was observed in patients with spKt/V <1.4 compared to those with spKt/V ≥1.4. This finding also implies a potential association between dialysis adequacy and inflammatory markers. Additionally, we previously demonstrated a high cytokine concentration in patients with both preexisting hypertension and long-COVID sequelae, indirectly suggesting a negative impact of chronic inflammation on long-term COVID-19 outcomes in this patient population.[37] Nonetheless, this complex interaction between chronic inflammation, dialysis adequacy, and long-term COVID-19 outcomes requires further investigation for a comprehensive understanding.

Third, the influence of a reduced dialysis dose on long-term COVID-19 outcomes can be viewed through the lens of comorbidity burden. A notable proportion of HD patients contend with comorbidities, encompassing conditions such as hypertension, cardiovascular events, and diabetes.[38,39] In our study cohort, a higher prevalence of these concurrent health issues was observed in patients with Kt/V<1.4 compared to the group achieving the Kt/V target. This observation emphasizes that our study cohort is not an exception and higher comorbidity burdens were evident in patients with suboptimal dialysis doses. These concurrent health issues introduce a multitude of complexities into the landscape of dialysis dosing. Challenges such as fluid overload, suboptimal vascular access, hemodynamic instability, and the use of multiple medications may hinder the efficient removal of uremic toxins during dialysis.[40–43] Also, comorbidities can exert a toll on a patient's nutritional status, potentially resulting in shifts in muscle mass and protein level.[44] Collectively, these factors contribute to a diminished dialysis dose, heightened mortality risk, and an increased susceptibility to severe acute COVID-19, and long-term COVID-19 outcomes.[19,39,45-48]

The study has several noteworthy limitations that should be acknowledged. First, its retrospective nature relies on historical data, which may introduce recall bias. Patients interpreted and reported their symptoms differently, potentially introducing bias in self-reported persistent symptoms and other subjective measures relevant to long-term COVID-19 outcomes. This variability in patient reporting could have impacted the accuracy of the collected data. Future studies could benefit from standardized data collection methods and cross-verification of self-reported symptoms with medical records or other objective measures to mitigate this variability in patient reporting. Second, the study primarily identifies associations between dialysis dose and long-term COVID-19 outcomes but does not establish causation.

Moreover, the relatively small sample size and regional characteristics of the study population may limit the generalizability of the findings to a broader HD population. Variations in patient demographics, healthcare practices, and resources at different centers could potentially influence the results. Larger, multicenter studies with diverse populations would enhance generalizability and provide a more comprehensive understanding of the associations. Third, despite efforts to exclude certain patients based on specific characteristics and comorbidities, there is a possibility of selection bias, and the excluded patients may have had different outcomes not considered in the analysis. Conducting sensitivity analyses or providing additional details on the characteristics of excluded patients could offer insights into the potential impact of selection bias on study outcomes. Additionally, the study's data covers a specific time frame, clinical practices and treatments for COVID-19 may have evolved during this period, potentially impacting outcomes. Furthermore, while the study focused on whether patients met a spKt/V target before contracting COVID-19, it did not investigate potential variability in dialysis dose over time, which could also influence outcomes. Future research could explore how changes in dialysis dose and inflammatory markers over time might impact long-term COVID-19 outcomes, providing a more nuanced understanding. Finally, due to the lack of information on socioeconomic status in the patient's medical records and the treatment of the acute phase of COVID-19 in specialized hospitals where data collection was not possible, the study did not account for factors such as socioeconomic status and the specific medications used in the acute treatment of COVID-19, which could potentially influence the observed results.

Nonetheless, despite the limitations our study is the first to shed light on the association between dialysis dose and one-year COVID-19 outcomes, underscoring the significance of optimizing dialysis therapy to protect patients undergoing HD from the potential long-term consequences of COVID-19. Based on these insights, we propose practical recommendations for physicians:

- prioritize regular monitoring of Kt/V levels aiming to achieve and maintain values at or above recommended targets;
- customize dialysis plans to cater to individual patient requirements, considering factors such as comorbidities, hypervolemic and nutritional statuses, suboptimal vascular access, hemodynamic instability, and others;
- reinforce infection prevention measures, including advocacy for COVID-19 vaccination;
- finally, impart education to patients on the paramount importance of adherence to dialysis prescriptions for overall improved outcomes.

Conclusion

In conclusion, our study highlights the crucial role of target dialysis dose, as measured by spKt/V values, in shaping the long-term outcomes of COVID-19 in patients undergoing HD. Achieving target spKt/V levels appears to confer protection against COVID-19 outcomes, including long-term sequelae, extended hospitalizations, and mortality. spKt/V threshold of ≤1.3 as a significant risk factor for both one-year hospitalization and mortality within our cohort. Further research is warranted to explore the intricate relationship between dialysis adequacy and COVID-19 outcomes, potentially offering new avenues for enhancing the care and prognosis of these patients.

Declarations

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Author contributions

Conceptualization, N.S.; Methodology, N.S..; Software, N.S.; Formal Analysis, N.S.; Data Curation, A.R. and L.S.; Writing – Original Draft Preparation, N..S. and A.R.; Writing – Review & Editing, N.S.

Conflicts of interest

The authors declare no competing financial support or interests.

Data availability

The data used in the study is available upon reasonable request to the corresponding author.

Ethics approval

The study protocol was approved by the Ethics Committee of the State Institution "Institute of Nephrology of the National Academy of Medical Sciences", Kyiv, Ukraine (protocol number: 2-2021, dated April 6, 2021).

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