OPEN

Vaccination and Nutritional Outcomes of Hemodialysis Patients Infected With SARS-CoV-2

Alberto Villaverde-Núñez ▾ María Teresa Ramírez-López ▾ Cristina Antón-Rodríguez ▾ Inés Constanze Hammel ▾ Cristina Pérez Ramos ▾ Miriam Álvarez Villarreal ▾ Sandra Ruíz Fernández ▾ Beatriz Arriero López ▾ Gema Hernández Cordobés ▾ Nemesio Manzano Guerrero ▾ Laura Baena Ruíz ▾ María Isabel Guerra-Llamas

Background: Patients on hemodialysis are particularly vulnerable to COVID-19 and may have a reduced response to vaccination because of a decreased immune response. The nutritional status before or during the infection could also impact on the clinical effectiveness of vaccination.

Objectives: We aim to describe the evolution of clinical and nutritional biomarkers of hemodialysis patients infected with SARS-CoV-2 and to assess their association with vaccination status.

Methods: An observational, analytic, longitudinal, retrospective multicenter study was carried out in 82 patients on hemodialysis with SARS-CoV-2 infection. Nutritional status was assessed using the Geriatric Nutritional Risk Index (GNRI), anthropometry, and biochemical parameters. The association of the vaccine doses with clinical- and nutritional-related variables was also evaluated.

Results: The percentage of vaccinated patients was similar to that of nonvaccinated patients. Before infection, most of the patients were malnourished. They presented lower albumin, creatinine, and urea levels than the well-nourished patients. Significant deterioration of nutritional status after infection was evidenced considering GNRI score, dry weight, and body mass index. Albumin and creatinine also decreased significantly after infection, whereas C-reactive protein increased in the acute phase. Significant inverse correlation was found between the variation of post–pre GNRI scores and basal albumin and C-reactive protein at 7 days. In addition, we observed the opposite trend between albumin at 30 days and basal cholesterol. A negative value in the GNRI variation was associated with bilateral pneumonia, need for hospitalization, and nutritional support. Vaccinated patients presented substantially less bilateral pneumonia and hospitalization. No significant effects were observed between vaccine doses and the variation in nutritional status, although a positive correlation was detected with the albumin at 7 days and C-reactive protein before infection and the number of vaccine doses received.

Discussion: COVID-19 is associated with affectations in the nutritional status and biomarkers in hemodialysis patients. In this study, vaccines have shown a protective effect against the clinical consequences of COVID. However, they have shown limitations in preventing the deterioration of nutritional status after infection. The results highlight the importance of promoting the vaccination in these patients as well as incorporating nutritional assessment before, during, and after the infection.

Key Words: COVID-19 • hemodialysis • nutritional status

Nursing Research, March/April 2024, Vol 73, No 2, 138–148

Alberto Villaverde-Núñez, MSN, RN, is Nephrology Nurse, Hospital Universitario del Henares, Madrid; and Infanta Sofia University Hospital and Henares University Hospital Foundation for Biomedical Research and Innovation (FIIB HUIS HHEN), Madrid, Spain.
María Teresa Ramírez-López, PhD, MSc, RN, is Professor, Faculty of Nursing, Physiotherapy and Podiatry, Universidad Complutense de Madrid, Spain.
Cristina Antón-Rodríguez, MD, MSc, is Professor, Faculty of Medicine, Universidad Francisco de Vitoria, Madrid, Spain.
Inés Constanze Hammel, PhD, MSc, RN, is R&D Nurse in Health Care, Hospital Universitario Infanta Sofía, Madrid, Spain.
Cristina Pérez Ramos, RN, is Nephrology Nurse, Hospital Universitario del Henares, Madrid, Spain.
Miriam Álvarez Villarreal, PhD, MSc, RN, is Nephrology Nurse, Hospital Universitario Infanta Cristina; and Professor, Faculty of Nursing, Universidad CEU San Pablo, Madrid, Spain.
Sandra Ruíz Fernández, RN, is Nephrology Nurse, Hospital Universitario del Sureste, Madrid, Spain.
Beatriz Arriero López, RN, is Nephrology Nurse, Hospital Universitario Infanta Sofía, Madrid, Spain.
Gema Hernández Cordobés, RN, is Nephrology Nurse, Hospital Universitario Infanta Cristina, Madrid, Spain.
Nemesio Manzano Guerrero, RN, is Nephrology Nurse, Hospital Universitario del Sureste, Madrid, Spain.
Laura Baena Ruíz, RN, is Nephrology Supervisor, Hospital Universitario del Henares, Madrid, Spain.
María Isabel Guerra-Llamas, PhD, MSN, RN, is Professor, Faculty of Nursing, Physiotherapy and Podiatry, Universidad Complutense de Madrid, Spain.

DOI: 10.1097/NNR.0000000000000707

INTRODUCTION

Patients with chronic kidney disease on renal replacement therapy with hemodialysis (HD) are considered a particularly at-risk population. The high comorbidity and uremic state produced by this illness may cause inflammation and immunosuppression (Betjes, 2013; Vaziri et al., 2012). This situation may increase the susceptibility to infections, such as that produced by the SARS-CoV-2 virus. Although the clinical symptoms of COVID-19 in HD patients are similar to the symptoms in patients without kidney disease, a significantly more severe course and a worse prognosis have been described in them after being infected with SARS-COV-2 (Aydin Bahat et al., 2020). Moreover, HD patients sometimes present an altered immune response to vaccines, as it has been shown with pneumococcal, hepatitis B, or influenza vaccines (Krueger et al., 2020). In the case of COVID-19, studies have shown a delayed and attenuated immune response in this population after vaccination (Chen et al., 2021; El Karoui & De Vriese, 2022; Van Praet et al., 2021).

In addition, it is important to note that nutritional alterations are frequent in HD patients. Indeed, calorie–protein malnutrition or protein-energy wasting (PEW) is a prevalent problem among HD patients, being present in 28%–54% of them (Carrero et al., 2018). It has been suggested that the risk of malnutrition may increase in these patients after being infected by COVID-19 (Pérez-Torres et al., 2021). However, to date, few studies have shown how the infection can affect the nutritional status in different phases of the infection. The scarcity of published studies on nutritional assessment in HD patients after infection with COVID-19 suggests that the characteristics of this pandemic have generated a series of barriers, which may have prevented the performance of routine nutritional assessments using validated tools for monitoring nutritional status such as the Geriatric Nutritional Risk Index (GNRI).

Recent research observed higher phosphate and albumin levels in HD patients who survived the disease (Min et al., 2021). Compared with those who died, this suggests that a better initial nutritional status may be protective. Some studies have also collected laboratory markers during infection that show alterations in nutritional status. Specifically, a decrease in serum albumin levels and an increase in C-reactive protein (CRP) levels have been identified among others (Aydin Bahat et al., 2020; Min et al., 2021). Recently, it has been described that there is a relationship between nutritional status and response to COVID-19 vaccination in HD patients. Specifically, it was observed that patients with malnutrition or low serum albumin levels had a worse response to vaccination, affecting the humoral and cellular responses to COVID-19 vaccines (Kwiatkowska et al., 2022; Lin et al., 2022; Van Praet et al., 2021).

Despite concerns about the efficacy of COVID-19 vaccines, recent studies have revealed that they may prevent infection, mitigate serious outcomes, and reduce the rate of hospitalizations in HD patients (Ashby et al., 2022; El Karoui & De Vriese, 2022; Oliver & Blake, 2022).

However, to date, it is unknown whether the number of doses received may attenuate the impact of infection on nutritional parameters in these patients, which are expected to be reduced after SARS-CoV-2 infection. Moreover, it remains unclear whether the COVID-19 vaccination in HD patients could impact the clinical course of the infection and the evolution of nutritional biomarkers through the different phases of the infection.

On the basis of this evidence, this study aims to describe the evolution of clinical and nutritional biomarkers of HD patients infected with SARS-CoV-2 and to assess their association with vaccination status. In addition, it seeks to detail the effects of vaccination against SARS-CoV-2 on common symptomatology and the need of hospitalization in the HD population.

MATERIALS AND METHODS

An observational, analytic, longitudinal, retrospective study was carried out in four HD units corresponding to four hospitals in Madrid (Spain): Henares Hospital, Infanta Sofía Hospital, Sureste Hospital, and Infanta Cristina Hospital. The study was approved by the Ethics Committee of the Hospital Universitario de La Princesa (Madrid, Spain), the research commissions that regulate research activity in the participating hospitals, and the research commission of the Faculty of Nursing, Physiotherapy, and Podiatry of the Complutense University of Madrid.

The selection of health centers was based on the similarity and the accessibility to the electronic records. We checked the totality of electronic records of HD patients in the four HD units from March 1, 2020, to February 1, 2022 ($n = 456$). The study included the patients infected for SARS-CoV-2 who met the following inclusion criteria: patients of both genders older than 18 years old, who had been on HD for more than 3 months, who were diagnosed with COVID-19 by reverse transcriptase polymerase chain reaction (PCR), and who could be followed up for a complete period (30 days before and 30 days after infection). Patients were excluded from the study if they had not been diagnosed by SARS-CoV-2 during the period studied and also if they had been admitted to a hospital in the 2 months before infection or had presented a severe acute intercurrent illness in the 4 weeks before or after infection. A final sample of 82 patients was ultimately achieved (Figure 1).

Data Collection and Tools

A research team, made up of trained nephrology nurses working in pairs in every hospital, was responsible for extracting the data from the electronic medical records. The data were supervised after the collection to check their accuracy before the data analysis.

Demographic, HD, and vaccination data were collected. The clinical characteristics of the infection were also recorded, focusing on respiratory and common gastrointestinal symptoms. In addition, the study evaluated the need for hospitalization, hospital stay duration, and the presence of death after

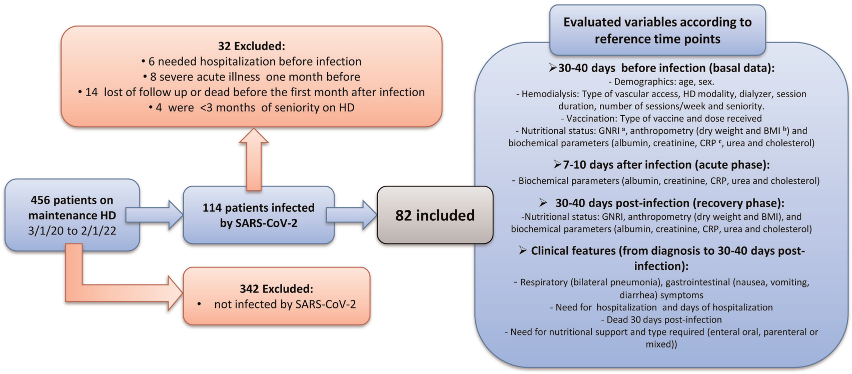

FIGURE 1. Participants and variables included in the study. HD = hemodialysis. [a]GNRI = Geriatric Nutritional Risk Index. [b]BMI = body mass index. [c]CRP = C-reactive protein.

30 days of infection. Nutritional status was assessed by GNRI and anthropometry (dry weight [DW] and body mass index [BMI]). DW was considered the lowest tolerated postdialysis weight achieved by a gradual change in postdialysis weight in which there are minimal signs or symptoms of hypovolemia or hypervolemia (Sinha & Agarwal, 2009). The GNRI was calculated by modifying the nutritional risk index for elderly patients (Bouillanne et al., 2005) using the equation proposed by Yamada et al. (2008) for HD patients. GNRI < 91.2 was taken as the cutoff point to identify malnourished patients (Yamada et al., 2008). From this cutoff point, the evolution of the patients' nutritional status was estimated (remaining nutritious, remaining malnourished, or experiencing either a worsening or an improvement in their nutritional status). Besides, the difference between the postinfection score and the previous total score was used to determine the GNRI variation variable, thereby expressing the evolution of the nutritional status after the infection. In addition, we evaluated some of the most relevant biochemical parameters extracted before the HD session. Three time points were taken as reference: 30–40 days before infection, when baseline data were collected; 7–10 days after infection, corresponding to the acute phase; and 30–40 days after infection, corresponding to the postinfection or recovery phase. In addition, we assessed the need for nutritional support and the type of support required (Figure 1).

Data Analysis

Analyses were performed using IBM SPSS Statistics 27 statistical software and GraphPad Prism 9.5.1. Qualitative variables were described as percentages and absolute frequencies, whereas quantitative variables were described with mean (*M*) and standard error of the mean (*SEM*) when they followed a normal distribution and with median and interquartile range otherwise. The Kolmogorov–Smirnov or Shapiro–Wilk test was applied to study the distribution of quantitative variables. The chi-square test was used to analyze differences between groups in qualitative variables. To analyze quantitative variables, Student *t* or analysis of variance, Mann–Whitney *U* or Kruskal–Wallis, Wilcoxon, or Friedman tests were used according to normality distribution, relationship between the variables, and number of groups to be compared, establishing the Bonferroni test for multiple comparisons. To study bivariate correlations between quantitative variables, Pearson (*R*) or Spearman (rho) correlations were studied according to normality. In all analyses, the significance level was set at $p \leq .05$.

RESULTS

Baseline Characteristics of Study Participants Before SARS-CoV-2 Infection

Eighty-two patients were included in the study. Most were men, with a mean age higher than 65 years. Most of them received HD through an arteriovenous fistula (72%), three sessions per week (91.5%), mainly through in-line hemofiltration (54.9%) versus conventional HD (45.1%) with high-permeability dialyzers.

A similar percentage of vaccinated and unvaccinated patients (51.2% vs. 48.8%) was found. Most vaccinated participants had received three doses (83.2%) with messenger RNA vaccines (Pfizer or Moderna [97.61%]; Table 1).

At baseline, most of the patients (68.1%) were malnourished before infection. They had significantly lower albumin ($p < .01$), creatinine ($p = .028$), and urea ($p = .005$) levels. The medians of CRP and cholesterol values were also lower in malnourished patients, although they did not show significant differences. In addition, we observed lower BMI and DW in malnourished patients before infection than in the well-nourished group, although these differences were not significant (Table 1).

Clinical Parameters of SARS-CoV-2 Infection in HD Patients

Considering the total patients included in the study ($N = 82$), 40.2% ($n = 33$) of infected patients had some symptoms, compared with 59.8% ($n = 49$) who were asymptomatic. A total of 25.6% ($n = 21$) developed bilateral pneumonia, and 15.9% ($n = 13$) had gastrointestinal symptoms. Among the patients who presented gastrointestinal symptoms, the most frequent was diarrhea in 53.8% ($n = 7$), followed by nausea (23.1%,

TABLE 1. Basal Characteristics of Participants

Characteristics		Total	Characteristics		Total
Demographic	Age (years), *M* (*SEM*)	67.5 (1.62)	Nutritional status (GNRI; *n* = 72)	*M* (*SEM*)	87.47 (0.88)
	Gender, *n* (%)			Malnourished (GNRI < 91.2), *n* (%)	49 (68.1)
	Male	53 (64.6)		Well nourished (GNRI > 91.2), *n* (%)	23 (31.9)
	Female	29 (35.4)			
Treatment	Vascular access, *n* (%)		Biochemical parameters	Albumin (g/dl), *Mdn* (IQR)**	
	CVC	23 (28)		Malnourished (GNRI < 91.2)	3 (0.55)
	AFV	59 (72)		Well nourished (GNRI > 91.2)	3.60 (0.55)
	Modality treatment, *n* (%)			Creatinine (mg/dl), *Mdn* (IQR)*	
	Conventional hemodialysis	37 (45.1)		Malnourished (GNRI < 91.2)	6.85 (2.39)
	Online hemodiafiltration	45 (54.9)		Well nourished (GNRI > 91.2)	7.56 (2.26)
	Number of sessions/week, *n* (%)			CRP (mg/dl), *Mdn* (IQR)	
	2	3 (3.7)		Malnourished (GNRI < 91.2)	5.65 (13.65)
	3	75 (91.5)		Well nourished (GNRI > 91.2)	9.46 (14.07)
	4	2 (2.4)		Urea (mg/dl), *Mdn* (IQR)**	
	6	2 (2.4)		Malnourished (GNRI < 91.2)	97 (46)
	Session duration (min), *Mdn* (IQR)	240 (30)		Well nourished (GNRI > 91.2)	119 (36)
	Seniority on HD (months), *Mdn* (IQR)	47.5 (43)		Cholesterol (mg/dl), *Mdn* (IQR)	
	Dialyzer, *n* (%)			Malnourished (GNRI < 91.2)	126 (43.25)
	Polyflux 210H	30 (36.6)		Well nourished (GNRI > 91.2)	127.5 (75.25)
	FX CorDiax 80	11 (13.4)			
	Phylther HF22SD	4 (4.9)	Anthropometric parameters	BMI (kg/m^2), *Mdn* (IQR)	25 (6)
	NS-21S	2 (2.4)		Malnourished (GNRI < 91.2)	25 (8)
	Solacea 21H	9 (11)		Well nourished (GNRI < 91.2)	26 (7)
	Elisio 21H	9 (11)			
	FX CorDiax 800	7 (8.5)		DW (kg), *Mdn* (IQR)	68 (22)
	Theranova 500	6 (7.3)		Malnourished (GNRI < 91.2)	64 (22)
	Others[a]	4 (4.9)		Well nourished (GNRI > 91.2)	70 (25)
SARS-CoV-2 vaccination	Doses received, *n* (%)				
	None	40 (48.8)			
	1	2 (2.4)			
	2	5 (6.1)			
	3	35 (42.7)			
	Type, *n* (%)				
	No	40 (48.8)			
	Pfizer-BioNTech[b]	15 (18.3)			
	Moderna[b]	26 (31.7)			
	Sinopharm[c]	1 (1.2)			

Note. Eighty-two participants were included in the study. *M* = mean; *SEM* = standard error of the mean; CVC = central venous catheter; AVF = arteriovenous fistula; min = minutes; *Mdn* = median; IQR = interquartile range; HD = hemodialysis; GNRI = Geriatric Nutritional Risk Index; CRP = C-reactive protein; BMI = body mass index; DW = dry weight.

[a]Others: Supra H7, LEOCEED-18H, SUREFLUX-19UX, and FX1000. [b]Messenger RNA vaccine. [c]Inactivated virus vaccine.

$^{*}p < .05$ and $^{**}p < .01$ after analysis by Mann–Whitney *U* test.

$n = 3$) and anorexia (23.1%, $n = 3$). A hospital admission rate of 30.5% ($n = 25$) for COVID-19 was observed in the patients studied, with a median hospital stay of 9.5 (interquartile range = 14) days. The percentage of patients who died after 30 days of infection was 4.88% ($n = 4$).

Analysis of the Effect of Infection on the Nutritional Status of HD Patients: Nutritional Status Assessment (GNRI) as well as Anthropometric and Biochemical Parameters

Nutritional Status Assessment (GNRI) We observed more malnourished than well-nourished patients before and after infection ($p = .014$; Figure 2A). Thirty days after infection, the number of malnourished patients increased to 85.7% ($n = 48$), decreasing the number of well-nourished patients to 14.3% ($n = 8$). Specifically, 17.9% ($n = 10$) of patients worsened their nutritional status, 67.9% ($n = 38$) remained malnourished, 8.9% remained well nourished ($n = 5$), and only 5.4% ($n = 3$) improved their nutritional status after infection. Considering the total GNRI score, a significant worsening in this value was shown after infection (Figure 2B).

In addition, significant differences were observed between the GNRI variation, which represents the difference between post and pre GNRI scores, and the nutritional status before infection ($p < .05$). These findings show that individuals who were well nourished before infection had a greater decrease in the GNRI variation variable, therefore indicating a greater worsening in GNRI values (Figure 2C). Despite the high percentages of malnutrition, only 25% (n = 16) required additional nutritional support; most of them received oral enteral nutrition (62.5%, n = 10), followed by parenteral nutrition (25%, n = 4); and only 12.5% (n = 2) required mixed nutrition (oral enteral and parenteral).

Anthropometric Parameters Regarding anthropometric variables, it was observed that, 30 days after infection, the DW was significantly lower (p = .008; Figure 2D). Similarly, BMI decreased significantly ($p < .01$) after the infection (Figure 2E).

Biochemical Parameters Biochemical parameters related to nutritional status were compared at three time points: baseline, on the seventh day after infection, and 30–40 days after the diagnosis of the infection. Considering the three periods studied, creatinine showed an almost significant downward trend (p = .056). Particularly, significant differences were evidenced between baseline creatinine and the creatinine values at 30–40 days after infection (p = .03; Figure 2F). In addition, we observed significant differences in the evolution of albumin through the different phases of the infection (p = .005). Specifically, a significant decrease was found when comparing basal albumin with albumin at 7–10 days after infection (p = .003) and between basal albumin and albumin at 30–40 days after infection (p = .025; Figure 2G). CRP also varied significantly (p = .006). Comparing the three time points, CRP significantly increased at 7 days after infection (p = .005) and significantly decreased at 30–40 days after infection (Figure 2H). However, regarding urea and cholesterol, no significant differences were found among the different points of infection measured.

Factors Associated With Nutritional Status Evaluated Through GNRI Variation: Demographic, HD Treatment, Clinical, Anthropometric, and Biochemical Parameters

To study the factors associated with a quantitative decrease in the GNRI score, the GNRI variation variable was analyzed as an indication of a worsening of nutritional status. A negative value of this variable indicated a worsening of nutritional status between the baseline situation and the situation 30–40 days after diagnosis of infection.

GNRI Variation and Demographic Factors No significant relationship was found between age and the variation in the GNRI score (p = .111). Moreover, no significant relationship

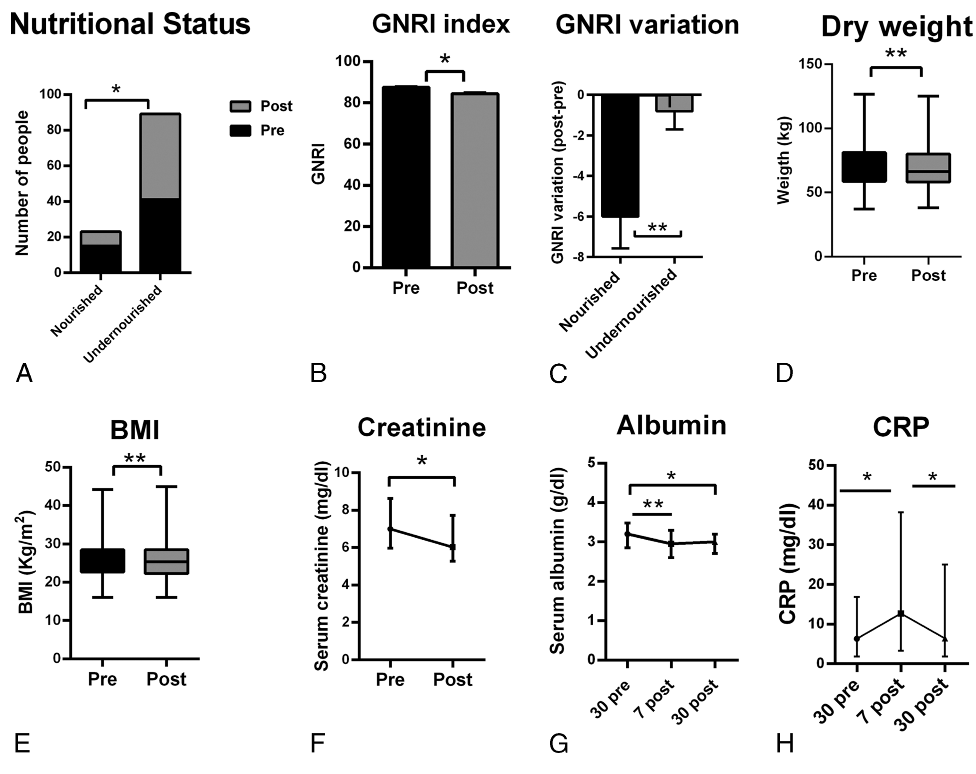

FIGURE 2. Effects of infection on hemodialysis patients in nutritional and biochemical parameters. The data are expressed as absolute frequency or as median and interquartile ranges or mean and standard error of the mean according to the normality test. (A) Chi-square test, *$p < .05$. (B and C) Student *t*-test, *$p < .05$ and **$p < .01$. (D–F) Wilcoxon test, **$p < .01$. (G and H) Friedman test with Bonferroni for multiple comparisons, *$p < .05$ and **$p < .01$. "Pre" indicates 30–40 days before infection, and "Post" indicates 30–40 days after the onset of infection. Values "7 post" and "30 post" indicate 7 days and 30–40 days after the diagnosis of infection, respectively. GNRI = Geriatric Nutritional Risk Index; BMI = body mass index; CRP = C-reactive protein.

was found between men and women in the variation of the GNRI score ($p = .721$).

GNRI Variation and HD Treatment Factors No relationship was found between GNRI variation and the type of vascular access ($p = .93$), treatment modality ($p = .1$) or type of dialyzer ($p = .236$), duration of HD sessions ($p = .79$), length of time in the HD program ($p = .54$), or number of dialysis sessions per week ($p = .69$).

GNRI Variation and Clinical Parameters Patients who experienced a worsening in their GNRI variation score and, consequently, in their nutritional status had more symptoms than patients with less variation, although the values were not significant ($p = .125$). A symptom-specific analysis revealed significant differences in GNRI variation in patients who develop bilateral pneumonia and patients who did not ($p = .009$; Figure 3A). However, no differences were found in the variation of GNRI between patients who presented gastrointestinal symptoms and those who did not ($p = .619$).

The GNRI variation was associated with the need for hospitalization. Patients who required hospital admission presented a lower value in the GNRI variation than those who did not ($p = .036$; Figure 3B). Regarding the patients who died, no differences were observed between those who died within 30 days after infection ($n = 4$) and the GNRI variation variable ($p = .178$).

Considering the need for nutritional support, the study showed that patients who required nutritional support presented a significantly ($p = .002$) more negative value in the GNRI variation than those who did not require it (Figure 3C). Moreover, differences were observed between the GNRI variation value and the type of nutritional support required ($p = .02$). Specifically, patients who required mixed nutritional support presented a significantly higher GNRI variation than patients who did not require it ($p = .004$; Figure 3D).

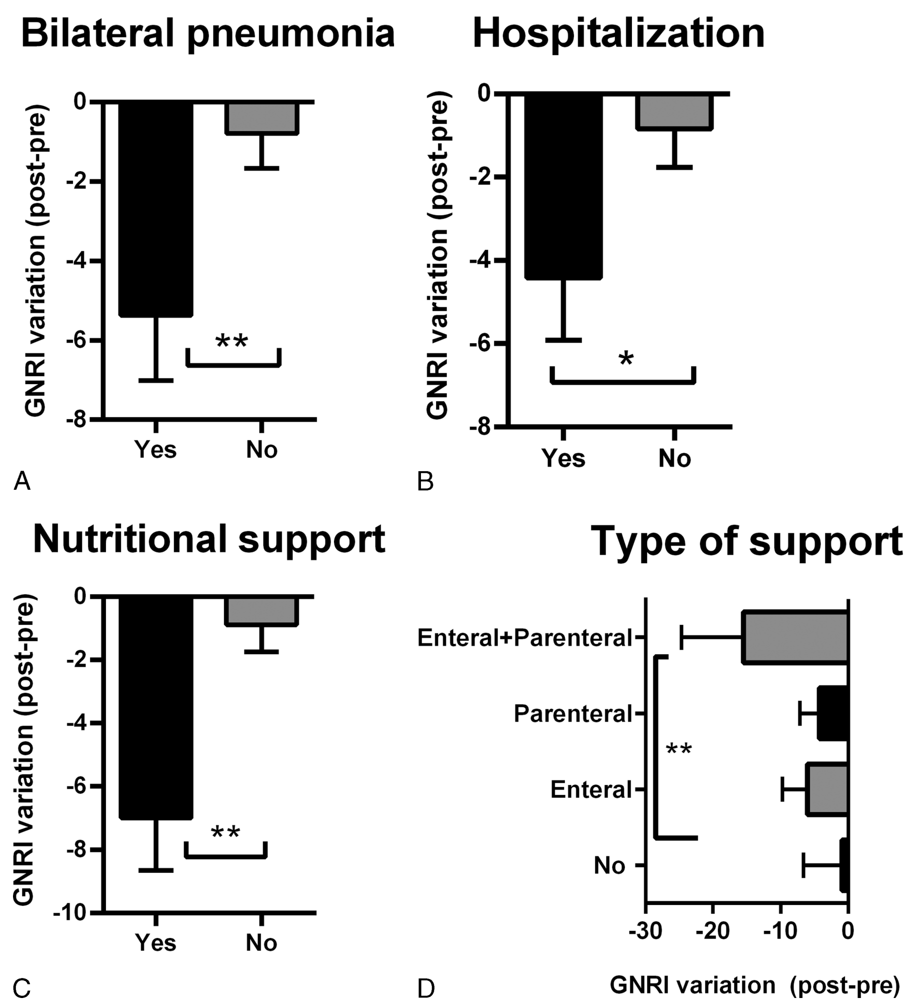

FIGURE 3. Relation of Geriatric Nutritional Risk Index (GNRI) variation to clinical consequences of COVID-19. The data are expressed as mean and standard error of the mean. (A–C) Student *t*-test, *$p < .05$ and **$p < .01$. (D) Analysis-of-variance test with Bonferroni for multiple comparisons, **$p < .01$.

GNRI Variation and Previous Anthropometric Parameters

No significant linear correlation was found between the variation of GNRI with baseline DW ($p = .65$) and that obtained 30–40 days after infection ($p = .45$) or with baseline BMI ($p = .61$) and that obtained 30–40 days after infection ($p = .318$).

GNRI Variation and the Evolution of Biochemical Parameters

An inverse correlation was observed between baseline albumin levels and GNRI variation, indicating that the higher preinfection albumin levels were associated to lower values in the variation of GNRI (indicating greater GNRI worsening). The opposite was found between GNRI variation and albumin at 30 days. In that case, the study showed a positive correlation, indicating that patients with a lower GNRI variation value (greater GNRI worsening) also had lower albumin levels 30 days after infection. We also observed an inverse correlation among baseline, 7–10 days, and 30 days postdiagnosis CRP levels and GNRI variation. On the other hand, a positive correlation was found between baseline cholesterol levels and GNRI variation. Finally, there was a trend toward direct relationships between basal urea levels and GNRI variation (Table 2).

Impact of SARS-CoV-2 Vaccination in HD Patients: Nutritional Status and Clinical Parameters

Relationship Between Vaccination and Nutritional Status and Biomarkers

No significant relationship was observed between the number of doses received and the worsening of nutritional status after infection, considering as worsening a decrease in the GNRI score ($p = .083$) or the qualitative variation (according to the cutoff point established to consider malnutrition [$p = .73$]). In addition, no relationship was found between the need for nutritional support and the number of vaccinations received ($p = .85$).

No significant correlations were observed between the number of doses received and the levels of basal albumin, albumin at 30–40 days of the infection, PCR at 7 days after infection, PCR at 30–40 days after infection, and creatinine, urea, and cholesterol levels at the different points of infection. However, a significant positive correlation was found between the number of vaccine doses and the albumin level at 7 days after infection (rho = 0.27, $p = .04$) and the CRP before infection (rho = 0.286, $p = .028$).

Impact of Vaccination on Clinical Parameters

The number of vaccine doses received up to the date of infection was related to the presence or absence of symptoms associated with the infection. Specifically, we observed that patients with symptomatic infection ($n = 33$) had received significantly fewer vaccine doses than those with mild and asymptomatic infection ($n = 49$; $p = .019$; Appendix Figure 1A, http://links.lww.com/NRES/A512). Within the symptoms, the presence of bilateral pneumonia ($n = 21$) was significantly lower in

TABLE 2. Correlation Between Geriatric Nutritional Risk Index Variation and Biochemical Parameters at Different Points of Infection

	GNRI variation	
Parameters	*p*-value	Correlation coefficient (*R* or rho)
Creatinine (mg/dl)		
Basal	.128	*R* = −.206
7–10 days after diagnosis	.898	Rho = 0.018
30–40 days after diagnosis	.767	Rho = 0.042
Albumin (g/dl)		
Basal	<.001***	*R* = −.456
7–10 days after diagnosis	.38	Rho = 0.144
30–40 days after diagnosis	.005**	Rho = 0.369
CRP (mg/dl)[a]		
Basal	.039*	Rho = −0.292
7–10 days after diagnosis	.042*	Rho = −0.289
30–40 days after diagnosis	.114	Rho = −0.231
Urea (mg/dl)		
Basal	.063	*R* = −.250
7–10 days after diagnosis	.556	Rho = 0.084
30–40 days after diagnosis	.394	*R* = −.118
Cholesterol (mg/dl)		
Basal	.044*	*R* = .298
7–10 days after diagnosis	.168	*R* = .291
30–40 days after diagnosis	.706	*R* = .064

Note. Data are expressed as correlation coefficients. *p*-Values are tested using Pearson's (*R*) correlation for variables with normal distribution and Spearman's correlation (rho) for those without normal distribution. CRP = C-reactive protein; GNRI = Geriatric Nutritional Risk Index.

*$p < .05$. **$p < .01$. ***$p < .001$.

vaccinated patients than in unvaccinated patients ($p < .001$; Appendix Figure 1B, http://links.lww.com/NRES/A512). In relation to gastrointestinal symptoms, it was found that the median number of doses received was higher in the group without gastrointestinal symptoms, although the differences were not significant ($p = .47$). When specifying the symptoms by type, we observed that the most frequent gastrointestinal symptom was diarrhea (n = 7), with a trend toward significance between doses received and the presence of this symptom ($p = .058$; Appendix 1C, http://links.lww.com/NRES/A512).

The need for hospital admission was substantially related to the number of vaccine doses received. Specifically, we found that the median number of doses received in patients who were admitted ($n = 25$) was lower than that in infected patients who did not require admission ($p = .001$; Appendix Figure 1D, http://links.lww.com/NRES/A512). An inverse relationship was observed between the number of doses received until infection and days of hospital stay, although the correlation was not significant ($p = .09$).

Finally, the mortality within 30 days after infection was lower in vaccinated patients than in unvaccinated patients, although these differences were not significant ($p = .258$; Appendix Figure 1E, http://links.lww.com/NRES/A512).

DISCUSSION

This is one of the first studies to assess the impact of COVID-19 infection in vaccinated and unvaccinated HD patients on clinical features and nutritional biomarkers through different points of the infection. Particularly, we have shown that the presence of bilateral pneumonia was significantly lower in vaccinated patients. These results corroborate recently published data by other authors showing the effectiveness of vaccination in the HD population in preventing severe outcomes and symptomatic diseases (El Karoui et al., 2022; Oliver & Blake, 2022; Tylicki et al., 2022). In addition, as other authors have shown (El Karoui & De Vriese, 2022; Oliver & Blake, 2022), we found that vaccination reduced the need for hospital admission. Moreover, we found that the number of vaccine doses received influenced the presence or absence of symptoms, supporting recent findings that show that the clinical efficacy of COVID-19 vaccination in HD patients increases substantially with the number of doses (Ashby et al., 2022; Falahi et al., 2022; Hernández-Porto et al., 2022). Therefore, studies such as ours could contribute to encourage vaccination among the unvaccinated population by adding new evidence of its efficacy in clinical samples.

In our study, a high percentage of participants had a poor basal nutritional status, higher than previously described in the literature in HD patients in other contexts (Carrero et al., 2018). This situation was also associated to lower basal albumin, creatinine, and urea levels. Considering that these patients were included in the study because they subsequently became infected by COVID-19, this high rate of malnutrition before infection could have increased vulnerability to infection. Particularly, nutritional alterations and the catabolic effect of uremia could have affected the immune response as previously suggested (Betjes, 2013; Fouque et al., 2008; Vaziri et al., 2012). On the other hand, these alterations together with the affectations in the biochemical parameters could have been associated with lower protein intake, muscle mass, and lower body protein (Carrero et al., 2014; Fouque et al., 2008). These aspects could explain the high percentage of malnourished patients before infection that we observed. Besides, they suggest the possibility of preventing infection by including adequate nutritional measures.

As a consequence of the infection, several biochemical parameters were found to be altered at different time points. Specifically, there was a significant decrease in creatinine 30 days after infection. This decrease could indicate a loss of muscle mass or, alternatively, a decrease in protein intake (Carrero et al., 2014). In addition, albumin levels that were suboptimal in a significant portion of the participants from the beginning decreased at 7 days after infection compared with baseline values. This decrease persisted at 30–40 days after infection. The trajectory of this marker could be showing a decrease in visceral protein reserves and/or protein intake. This, together with the decrease in creatinine, may also be explicative of the PEW or malnutrition after infection. In contrast, we found that the CRP values increased from baseline data in the acute phase of infection and decreased after the infection. Likewise, other authors have found similar results in albumin and CRP (Chaudhuri et al., 2022). These biochemical modifications could also help to understand the physiological changes caused by SARS-CoV-2 in HD patients.

A significant deterioration of nutritional status was evidenced by a decrease in DW, BMI, and GNRI total score after infection. Paradoxically, the study showed that people with better baseline nutritional status experienced the greatest decrease in the GNRI score. Despite this, the total GNRI score after infection in this group of well-nourished patients was higher than that in the group that had been malnourished, being close to the margin of moderate malnutrition (GNRI = 82–92). In contrast, the previously malnourished patients' level remained close to that considered severe malnutrition (GNRI < 82; Silva et al., 2020). This could indicate that a better baseline nutritional status, although not preventing the nutritional deterioration after infection, could mitigate the intimidation that implies the COVID-19. On the other hand, considering basal biomarkers, it was also observed that albumin and CRP showed an inverse correlation between their baseline levels and this variable, whereas cholesterol showed a positive correlation. This indicates that patients with higher albumin and CRP levels before infection and patients with lower prior cholesterol levels were the patients in whom the GNRI score decreased the most. Regarding albumin, the data contrast with previous research, which shows that generally decreased values of albumin represent a worse prognosis in renal patients and in patients infected with SARS-CoV-2 in general (Don & Kaysen, 2004; Hariyanto et al., 2021). However, low cholesterol levels have been considered indicators of inflammation and malnutrition and may decline the prognosis of some pathologies in these patients (Chiang et al., 2005; Lin et al., 2022; Liu et al., 2004). Similarly, previous elevated CRP could indicate a basal inflammatory state, and its higher levels have been associated with a worse prognosis to infection (Hariyanto et al., 2021). The data point out that the inflammatory state before infection could increase these patients' vulnerability to the infection itself and to the worsening of their nutritional status. Future studies with larger samples may confirm these ideas. On the other hand, the data suggest that monitoring and improve the nutrition of HD patients before infection or shortly after diagnosis could be successful strategies to prevent a stronger nutritional deterioration (Pérez-Torres et al., 2021).

In addition, we observed a positive correlation between GNRI worsening and albumin values at 30–40 days, indicating that patients with more GNRI variation had lower albumin levels at the end of the infection. These aspects have been associated with a worse nutritional status and prognosis (Min et al., 2021). However, despite the deterioration of the GNRI, only 25% of the patients needed some type of nutritional support. Particularly, those who received this support were those who presented the greatest negative variation of the GNRI. This fact shows that the most severe cases of nutritional deterioration were detected and treated with different types of nutritional support. Furthermore, among them, we observed that the most invasive nutritional support (enteral and parenteral nutrition) was prescribed in the presence of very high GNRI variations (significant worsening of nutritional status). An inverse correlation was also found between GNRI worsening and CRP values after infection. It should be noted that low levels of albumin and higher values of CRP have been associated with a worse prognosis of the infection. Thus, several authors have shown that HD patients who have died or who presented a more severe COVID-19 infection may have had lower albumin levels and higher CRP levels than survivors (Hariyanto et al., 2021). Considering that, in our study, these parameters were associated to the deterioration of nutritional status. The data support the idea of ensuring adequate nutrition in these patients, which could influence other adverse effects associated to COVID-19 infection (Izcovich et al., 2020; Min et al., 2021).

Regarding the presence of symptoms and their relationship with nutritional status, the study revealed that patients who were more nutritionally deteriorated after infection, those who presented a greater variation in GNRI, showed bilateral pneumonia and were hospitalized more frequently. Both associations remark the relationship between the worsening of nutritional status with the most severe form of the disease in HD patients, supporting the hypotheses proposed by other authors (Pérez-Torres et al., 2021).

On the other hand, in our study, we failed to find an association between the number of vaccine doses received and the deterioration of GNRI. The data highlight the necessity to look for alternative ways to prevent nutritional deterioration in these patients. Despite this, a positive low correlation was found between the number of doses of vaccine and the levels of albumin during the infection and the CRP before infection. Although the positive correlation between the number of vaccine doses and CRP before infection may have a paradoxical result, the positive albumin correlation with the number of vaccine doses suggests a discrete positive effect of vaccination in these patients. This may be mediated by an increased antibody titer, as it has been described (Agur et al., 2021). Further research may confirm these hypotheses.

Some limitations should be considered in this work. Because the data were obtained retrospectively and considering the conditions of the pandemic, especially during the first wave, certain data could not be recorded. The inclusion criteria that considered the patients as participants only when it was possible to complete the follow-up at 30 days may have limited the sample size. This may have consequently impacted the significance of some results. However, this study provides new evidence regarding the protective effect of vaccination against COVID-19 and the effect of the infection on the evolution of nutritional-related parameters in HD patients.

In conclusion, HD patients present a high degree of malnutrition, which is even more accentuated after infection. Specifically, there is a significant decrease in GNRI score, DW, BMI, albumin, and serum creatinine levels with an increase in CRP levels after infection. All these are indicative that HD patients are at a high risk of PEW or malnutrition after COVID-19. Some biomarkers that indicate a deterioration in nutritional status, at the expense of a decrease in the GNRI score, include higher albumin and lower cholesterol levels before infection as well as higher CRP levels before infection and 7 days after infection. In this study, the vaccines have shown clinical efficacy and a protective effect against the virus in HD patients. Particularly, the number of vaccine doses received has been associated with the presence of symptoms, the development of bilateral pneumonia, the need for hospital admission, and the levels of albumin during the infection. However, this number of doses has not been found to prevent the alteration of the overall nutritional status after the infection.

Overall, the data show the importance of addressing nutritional aspects to improve the repercussions of infection in these patients as well as promoting vaccination in them.

Accepted for publication September 28, 2023.

María Teresa Ramírez-López and María Isabel Guerra-Llamas share senior authorship.

The authors thank the participating patients who have made this study possible and Sara Pintado for reviewing this article for English language. This work has been funded by the Foundation for Biomedical Research and Innovation of the Infanta Sofía University Hospital and Henares University Hospital (FIIB HUIS HHEN), Madrid, Spain.

The authors have no conflicts of interest to disclose.

Corresponding author: María Teresa Ramírez López, PhD, MSc, RN, Faculty of Nursing, Physiotherapy and Podiatry, Universidad, Complutense de Madrid, Madrid, Spain (e-mail: mt.ramirez@ucm.es).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.nursingresearchonline.com).

ORCID iDs

Alberto Villaverde-Núñez https://orcid.org/0000-0002-1352-4909
María Teresa Ramírez López https://orcid.org/0000-0002-3944-5264
Cristina Antón Rodríguez https://orcid.org/0000-0001-8218-9780
Inés Constanze Hammel https://orcid.org/0000-0001-5962-756X
Cristina Pérez Ramos https://orcid.org/0009-0000-8800-0803
Miriam Álvarez Villarreal https://orcid.org/0000-0003-3244-2922
Sandra Ruíz Fernández https://orcid.org/0000-0002-7044-9511
Beatriz Arriero López https://orcid.org/0000-0003-1187-5091
Gema Hernández Cordobés https://orcid.org/0000-0001-7806-8919
Nemesio Manzano Guerrero https://orcid.org/0000-0003-1669-1291
Laura Baena Ruíz https://orcid.org/0000-0003-4126-5884
María Isabel Guerra Llamas https://orcid.org/0000-0003-2176-2664

REFERENCES

Agur, T., Ben-Dor, N., Goldman, S., Lichtenberg, S., Herman-Edelstein, M., Yahav, D., Rozen-Zvi, B., & Zingerman, B. (2021). Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients—A prospective cohort study. *Nephrol Dial Transplant*, *36*, 1347–1349. https://doi.org/10.1093/ndt/gfab155

Ashby, D. R., Caplin, B., Corbett, R. W., Asgari, E., Kumar, N., Sarnowski, A., Hull, R., Makanjuola, D., Cole, N., Chen, J., Nyberg, S., McCafferty, K., Zaman, F., Cairns, H., Sharpe, C., Bramham, K., Motallebzadeh, R., Anwari, K. J., Salama, A. D., & Banerjee, D., Pan-London COVID-19 Renal Audit Group. (2022). Severity of COVID-19 after vaccination among hemodialysis patients: An observational cohort study. *Clinical Journal of the American Society of Nephrology*, *17*, 843–850. https://doi.org/10.2215/CJN.16621221

Aydin Bahat, K., Parmaksiz, E., & Sert, S. (2020). The clinical characteristics and course of COVID-19 in hemodialysis patients. *Hemodialysis International*, *24*, 534–540. https://doi.org/10.1111/hdi.12861

Betjes, M. G. (2013). Immune cell dysfunction and inflammation in end-stage renal disease. *Nature Reviews Nephrology*, *9*, 255–265. https://doi.org/10.1038/nrneph.2013.44

Bouillanne, O., Morineau, G., Dupont, C., Coulombel, I., Vincent, J.-P., Nicolis, I., Benazeth, S., Cynober, L., & Aussel, C. (2005). Geriatric Nutritional Risk Index: A new index for evaluating at-risk elderly medical patients. *The American Journal of Clinical Nutrition*, *82*, 777–783. https://doi.org/10.1093/ajcn/82.4.777

Carrero, J. J., Chen, J., Kovesdy, C. P., & Kalantar-Zadeh, K. (2014). Critical appraisal of biomarkers of dietary intake and nutritional status in patients undergoing dialysis. *Seminars in Dialysis*, *27*, 586–589. https://doi.org/10.1111/sdi.12283

Carrero, J. J., Thomas, F., Nagy, K., Arogundade, F., Avesani, C. M., Chan, M., Chmielewski, M., Cordeiro, A. C., Espinosa-Cuevas, A., Fiaccadori, E., Guebre-Egziabher, F., Hand, R. K., Hung, A. M., Ikizler, T. A., Johansson, L. R., Kalantar-Zadeh, K., Karupaiah, T., Lindholm, B., Marckmann, P., … Kovesdy, C. P. (2018). Global prevalence of protein-energy wasting in kidney disease: A meta-analysis of contemporary observational studies from the International Society of Renal Nutrition and Metabolism. *Journal of Renal Nutrition*, *28*, 380–392. https://doi.org/10.1053/j.jrn.2018.08.006

Chaudhuri, S., Lasky, R., Jiao, Y., Larkin, J., Monaghan, C., Winter, A., Neri, L., Kotanko, P., Hymes, J., Lee, S., Wang, Y., Kooman, J. P., Maddux, F., & Usvyat, L. (2022). Trajectories of clinical and laboratory characteristics associated with COVID-19 in hemodialysis patients by survival. *Hemodialysis International*, *26*, 94–107. https://doi.org/10.1111/hdi.12977

Chen, J.-J., Lee, T. H., Tian, Y.-C., Lee, C.-C., Fan, P.-C., & Chang, C.-H. (2021). Immunogenicity rates after SARS-CoV-2 vaccination in people with end-stage kidney disease: A systematic review and meta-analysis. *JAMA Network Open*, *4*, e2131749. https://doi.org/10.1001/jamanetworkopen.2021.31749

Chiang, C.-K., Ho, T.-I., Hsu, S.-P., Peng, Y.-S., Pai, M.-F., Yang, S.-Y., Hung, K.-Y., & Tsai, T.-J. (2005). Low-density lipoprotein cholesterol: Association with mortality and hospitalization in hemodialysis patients. *Blood Purification*, *23*, 134–140. https://doi.org/10.1159/000083529

Don, B. R., & Kaysen, G. (2004). Serum albumin: Relationship to inflammation and nutrition. *Seminars in Dialysis*, *17*, 432–437. https://doi.org/10.1111/j.0894-0959.2004.17603.x

El Karoui, K., & De Vriese, A. S. (2022). COVID-19 in dialysis: Clinical impact, immune response, prevention, and treatment. *Kidney International*, *101*, 883–894. https://doi.org/10.1016/j.kint.2022.01.022

El Karoui, K., Hourmant, M., Ayav, C., Glowacki, F., Couchoud, C., & Lapidus, N., REIN Registry. (2022). Vaccination and COVID-19 dynamics in dialysis patients. *Clinical Journal of the American Society of Nephrology*, *17*, 395–402. https://doi.org/10.2215/CJN.10300721

Falahi, S., Sayyadi, H., & Kenarkoohi, A. (2022). Immunogenicity of COVID-19 mRNA vaccines in hemodialysis patients: Systematic review and meta-analysis. *Health Science Reports*, *5*, e874. https://doi.org/10.1002/hsr2.874

Fouque, D., Kalantar-Zadeh, K., Kopple, J., Cano, N., Chauveau, P., Cuppari, L., Franch, H., Guarnieri, G., Ikizler, T. A., Kaysen, G., Lindholm, B., Massy, Z., Mitch, W., Pineda, E., Stenvinkel, P., Treviño-Becerra, A., & Wanner, C. (2008). A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney International*, *73*, 391–398. https://doi.org/10.1038/sj.ki.5002585

Hariyanto, T. I., Japar, K. V., Kwenandar, F., Damay, V., Siregar, J. I., Lugito, N. P. H., Tjiang, M. M., & Kurniawan, A. (2021). Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: A systematic review and meta-analysis. *The American Journal of Emergency Medicine*, *41*, 110–119. https://doi.org/10.1016/j.ajem.2020.12.076

Hernández-Porto, M., García, S., Delgado, T., Rodriguez, Y., Aguirre-Jaime, A., Campos, S., Hernández, C., Lorenzo, C., & Lecuona, M. (2022). Humoral response to SARS-CoV-2 after vaccination and booster effect in patients undergoing dialysis. *International*

Journal of Infectious Diseases, *122*, 327–331. https://doi.org/10.1016/j.ijid.2022.05.065

Izcovich, A., Ragusa, M. A., Tortosa, F., Lavena Marzio, M. A., Agnoletti, C., Bengolea, A., Ceirano, A., Espinosa, F., Saavedra, E., Sanguine, V., Tassara, A., Cid, C., Catalano, H. N., Agarwal, A., Foroutan, F., & Rada, G. (2020). Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLOS ONE*, *15*, e0241955. https://doi.org/10.1371/journal.pone.0241955

Krueger, K. M., Ison, M. G., & Ghossein, C. (2020). Practical guide to vaccination in all stages of CKD, including patients treated by dialysis or kidney transplantation. *American Journal of Kidney Diseases*, *75*, 417–425. https://doi.org/10.1053/j.ajkd.2019.06.014

Kwiatkowska, E., Safranow, K., Wojciechowska-Koszko, I., Roszkowska, P., Dziedziejko, V., Myślak, M., Różański, J., Ciechanowski, K., Stompór, T., Przybyciński, J., Wiśniewski, P., Kwella, N., Kwiatkowski, S., Prystacki, T., Marcinkowski, W., & Domański, L. (2022). SARS-CoV-2 mRNA vaccine-induced cellular and humoral immunity in hemodialysis patients. *Biomedicine*, *10*, 636. https://doi.org/10.3390/biomedicines10030636

Lin, T.-Y., Hung, N.-K., & Hung, S.-C. (2022). Association of malnutrition with SARS-CoV-2 vaccine response in patients undergoing hemodialysis. *Clin Nutr*, *41*, 2683–2690. https://doi.org/10.1016/j.clnu.2022.10.011

Liu, Y., Coresh, J., Eustace, J. A., Longenecker, J. C., Jaar, B., Fink, N. E., Tracy, R. P., Powe, N. R., & Klag, M. J. (2004). Association between cholesterol level and mortality in dialysis patients: Role of inflammation and malnutrition. *JAMA*, *291*, 451–459. https://doi.org/10.1001/jama.291.4.451

Min, Y., Cheng, L., Tu, C., Li, H., He, D., Huang, D., Chen, D., Huang, X., Chen, F., & Xiong, F. (2021). Clinical characteristics of deceased hemodialysis patients affected by COVID-19. *International Urology and Nephrology*, *53*, 797–802. https://doi.org/10.1007/s11255-020-02700-x

Oliver, M. J., & Blake, P. G. (2022). Clinical utility of COVID-19 vaccination in patients undergoing hemodialysis. *Clinical Journal of the American Society of Nephrology*, *17*, 779–781. https://doi.org/10.2215/CJN.04930422

Pérez-Torres, A., Caverni Muñoz, A., Lou Arnal, L. M., Sanz Paris, A., Vidal Peracho, C., La Torre Catalá, J., Sánchez Villanueva, R., Cigarrán Guldris, S., Trocoli González, F., Nogueira Pérez, Á., Sanjurjo Amado, A., González García, M. E., & Barril Cuadrado, G. (2021). Multidisciplinary nutritional consensus on assessment and nutritional dietary treatment in patients with chronic kidney disease and SARS-CoV-2 infection. *Nefrología*, *41*, 453–460. https://doi.org/10.1016/j.nefroe.2021.10.002

Silva, D. F. O., Lima, S. C. V. C., Sena-Evangelista, K. C. M., Marchioni, D. M., Cobucci, R. N., & Andrade, F. B. (2020). Nutritional risk screening tools for older adults with COVID-19: A systematic review. *Nutrients*, *12*, 2956. https://doi.org/10.3390/nu12102956

Sinha, A. D., & Agarwal, R. (2009). Can chronic volume overload be recognized and prevented in hemodialysis patients? The pitfalls of the clinical examination in assessing volume status. *Seminars in Dialysis*, *22*, 480–482. https://doi.org/10.1111/j.1525-139X.2009.00641.x

Tylicki, L., Biedunkiewicz, B., Puchalska-Reglińska, E., Gellert, R., Burnier, M., Wolf, J., & Dębska-Ślizień, A. (2022). COVID-19 vaccination reduces mortality in patients on maintenance hemodialysis. *Frontiers in Medicine*, *9*, 937167. https://doi.org/10.3389/fmed.2022.937167

Van Praet, J., Reynders, M., De Bacquer, D., Viaene, L., Schoutteten, M. K., Caluwé, R., Doubel, P., Heylen, L., De Bel, A. V., Van Vlem, B., Steensels, D., & De Vriese, A. S. (2021). Predictors and dynamics of the humoral and cellular immune response to SARS-CoV-2 mRNA vaccines in hemodialysis patients: A multicenter observational study. *Journal of the American Society of Nephrology: JASN*, *32*, 3208–3220. https://doi.org/10.1681/ASN.2021070908

Vaziri, N. D., Pahl, M. V., Crum, A., & Norris, K. (2012). Effect of uremia on structure and function of immune system. *Journal of Renal Nutrition*, *22*, 149–156. https://doi.org/10.1053/j.jrn.2011.10.020

Yamada, K., Furuya, R., Takita, T., Maruyama, Y., Yamaguchi, Y., Ohkawa, S., & Kumagai, H. (2008). Simplified nutritional screening tools for patients on maintenance hemodialysis. *The American Journal of Clinical Nutrition*, *87*, 106–113. https://doi.org/10.1093/ajcn/87.1.106