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Original article

Association of malnutrition with SARS-CoV-2 vaccine response in patients undergoing hemodialysis

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SUMMARY

Background & aims: Patients undergoing dialysis are less likely to develop immune responses to SARS-CoV-2 vaccine. Malnutrition is common in the dialysis population. However, whether malnutrition contributes to the impaired immunogenicity remains unknown. The aim of this study was to assess the association between nutritional status and SARS-CoV-2 vaccine response in patients receiving maintenance hemodialysis.

Methods: A total of 206 hemodialysis patients (mean age, 67 ± 13 years) without prior SARS-CoV-2 infection were examined for the primary outcome of seroconversion, defined as the detection of IgG antibodies (≥50 AU/mL) to the receptor-binding domain of the S1 spike protein of SARS-CoV-2 one month after a priming dose of ChAdOx1 nCoV-19, an adenovirus-vectored vaccine. Nutritional status was assessed by using the Controlling Nutritional Status (CONUT) score, an objective indicator of nutrition incorporating serum albumin, total cholesterol, and total lymphocyte count, as well as the subjective global assessment (SGA).

Results: Overall, 16.5% of patients were classified as malnourished, and 64.1% of patients were at risk for malnutrition based on the CONUT score. Anti-SARS-CoV-2 IgG were the highest in patients with normal nutrition. In multivariate logistic regression analyses adjusted for age, sex, comorbidities, and use of immunosuppressants, patients with malnutrition remained less likely to develop an antibody response than those with normal nutrition (odds ratio 0.23, 95% CI, 0.07–0.76). SGA was a significant predictor of anti-SARS-CoV-2 IgG seroconversion in univariate but not multivariate analyses.

Conclusions: Malnutrition according to CONUT score is associated with impaired humoral responses to SARS-CoV-2 vaccination in patients undergoing hemodialysis. Our results highlight the importance of incorporating nutritional assessment into routine dialysis care to identify patients at risk for suboptimal immune responses after SARS-CoV-2 vaccination. Further research is needed to determine whether nutritional intervention can improve immune responses in these vulnerable patients.

1. Introduction

Patients with end-stage kidney disease (ESKD) undergoing long-term dialysis are at higher risk of infection and adverse outcomes from coronavirus disease 2019 (COVID-19), which is especially true in those with older age, higher body mass index (BMI), and comorbid conditions such as diabetes and cardiovascular diseases [1]. Vaccination is effective and essential to control the COVID-19 pandemic [2], but immunogenicity to vaccines is often attenuated in dialysis patients [3,4]. A recent systematic review and meta-analysis demonstrated that patients receiving dialysis had a significantly poorer antibody response rate following vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than did those not receiving dialysis, particularly after the first dose [5]. In addition, despite the high availability and coverage of COVID-19 vaccines, a substantial proportion of patients receiving dialysis are hesitant to seek COVID-19 vaccination [6]. A recent study has provided evidence

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CONUT, controlling nutritional status; COVID-19, coronavirus disease 2019; ESKD, end-stage kidney disease; KDOQI, Kidney Disease/Dialysis Outcomes and Quality Initiative; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGA, subjective global assessment.

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that vaccine hesitancy was mainly due to a lack of confidence in efficacy and concerns about safety [7]. Identifying factors that are associated with a favorable vaccine response may improve vaccine uptake in these susceptible patients.

Malnutrition is highly prevalent and is associated with poor outcomes among dialysis patients [8]. Uremia-induced nutritional and catabolic alterations, such as inadequate intake, loss of nutrients during dialysis, metabolic acidosis, endocrine disorders, and inflammation, may affect the normal immune system [9]. It has been shown that poor nutritional status, as mostly detected by serum albumin levels, was associated with an impaired immune response following hepatitis B virus vaccination among dialysis patients [3]. Serum albumin has also been identified as an independent predictor of immune responses to COVID-19 vaccination in patients treated with dialysis [10]. However, no single biomarkers are sufficiently reliable or valid to use in isolation for assessing nutritional status, as they are influenced by nonnutritional factors, especially in patients on maintenance dialysis [11]. Instead, a more comprehensive evaluation is recommended by the 2020 Kidney Disease/Dialysis Outcomes and Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in chronic kidney disease [12]. Moreover, mounting evidence has indicated the role of malnutrition in predicting poorer COVID-19 outcomes [13,14]. Therefore, our objective in the present study was to determine the association of nutritional status, assessed by using the Controlling Nutritional Status (CONUT) score and the 7-point subjective global assessment (SGA), with humoral immune responses following COVID-19 vaccination in patients undergoing hemodialysis.

2. Materials and methods

2.1. Study design and patients

This was a prospective cohort study involving prevalent hemodialysis patients from the hemodialysis unit of Taipei Tzu Chi Hospital, Taiwan. Adult patients aged over 20 years and older who had no history of laboratory-confirmed SARS-CoV-2 infection or of COVID-19-like symptoms, such as fever, sore throat, cough, or loss of taste or smell, were eligible for inclusion. We did not assess anti-SARS-CoV-2 antibodies at baseline because, during the study period, a combination of case-based (including contact tracing and quarantine) and population-based (including social distancing and facial masking with wide adherence) interventions has been extraordinarily successful in containing COVID-19 in Taiwan [15]. Exclusion criteria included previous vaccination against SARS-CoV-2, refusal of vaccination, inadequate dialysis, and refusal to participate in the study. All patients were vaccinated with the ChAdOx1 nCoV-19 vaccine on June 16 or 17, 2021, and followed until July 15, 2021. The vaccines were distributed directly to the dialysis center and were administered at a dose of 5×10^{10} viral particles as a single injection into the deltoid muscle after dialysis. This study complied with the Declaration of Helsinki and was approved by the institutional review board of Taipei Tzu Chi Hospital (10-XD-117). All patients gave their written informed consent.

2.2. Data collection and measurements

Information on demographics and comorbidities was obtained from patient interviews and chart reviews at the time of study enrollment. Diabetes mellitus was defined as a self-reported history or the use of antidiabetic agents including insulin. Hypertension was defined as predialysis blood pressure >140/90 mm Hg on the day of vaccination or the use of antihypertensive medications. The presence of coronary artery disease (CAD) was based on coronary angiography or based on a history of myocardial infarction. The maintenance immunosuppressant regimen included glucocorticoids, calcineurin inhibitors, antimetabolites, and biological agents. Blood samples were collected from patients who had fasted overnight before the mid-week dialysis session. The serum albumin concentration was determined by using the bromocresol green method. Total cholesterol was measured using an enzymatic assay. Complete blood counts were performed by an autoanalyzer (XE-2100, Sysmex, Kobe, Japan). Patients underwent anthropometric measurements 30 min after the hemodialysis session. Body weight and height were determined using standardized procedures; BMI was calculated as body weight in kilograms divided by height in meters squared.

2.3. Nutritional status assessments

The nutritional status of each patient was evaluated at baseline using two approaches: the CONUT score and the 7-point SGA.

2.3.1. CONUT

The CONUT score, originally developed to assess the nutritional status of hospitalized patients by Ulibarri et al. [16], has been demonstrated to be predictive of all-cause mortality in peritoneal dialysis patients and dialysis patients undergoing endovascular therapy for peripheral artery disease [17,18]. The CONUT score is calculated from serum albumin, total cholesterol, and total lymphocyte count (Supplemental Table 1). Patients were grouped according to their composite CONUT score as follows: normal nutritional status (scores 0–1), at risk of malnutrition (scores 2–4), and malnutrition (scores 5–8). These cutoffs were selected a priori and were previously validated against the SGA [16].

2.3.2. SGA

The SGA is a valid tool recommended by the K/DOQI for assessing the nutritional status of dialysis patients [12]. Based on the clinical judgment, a registered dietitian assessed a patient's history of recent weight change, dietary intake, and gastrointestinal symptoms and conducted a physical examination of loss of subcutaneous fat and muscle wasting. The overall assessment was scored from 1 to 7. Patients were assigned a rating of severe malnutrition (scores 1–3), moderate malnutrition (scores 4–5), or a normal nutritional status (scores 6–7). These cutoffs were independently associated with increased mortality in chronic dialysis patients [19].

2.4. Immunogenicity assessments

On Day 28 after a priming dose of the ChAdOx1 nCoV-19 vaccine, humoral immune responses were assessed [20]. IgG antibodies to the receptor-binding domain of the S1 subunit of the spike protein (anti–S1-RBD IgG) of SARS-CoV-2 were determined in serum using the AdviseDx SARS-CoV-2 IgG II assay (Abbot Laboratories, Abbott Park, IL). A value of $\geq$50 arbitrary units per milliliter (AU/mL) was considered positive [21]. The measurement of neutralizing antibodies was undertaken using the MeDiPro SARS-CoV-2 Antibody ELISA (Formosa Biomedical Technology, Taipei, Taiwan). Values of $\geq$12.31 IU/mL (50% neutralizing titer [NT_{50}] $\geq$ 2.56) were defined as a positive response.

2.5. Reactogenicity and safety assessments

Solicited local (pain, redness, and swelling) and systemic reactions (fatigue, headache, muscle and joint pain, nausea or vomiting, abdominal pain, diarrhea, and fever [defined as body temperature $\geq$38 °C]) that occurred within 7 days after receiving ChAdOx1 nCoV-19 were recorded by the patient's primary nurse

using a questionnaire established by the Taiwan Centers for Disease Control. Data on unsolicited adverse events and severe adverse events were collected for 28 days following vaccination.

2.6. Exposure and outcome

The main exposure was nutritional status defined by the CONUT score. Patients were categorized as having a normal nutritional status, being at risk of malnutrition, and having malnutrition based on their CONUT score. Nutritional status according to the 7-point SGA was investigated as a secondary exposure. The outcome of interest was the serological response, defined as anti-spike IgG levels ≥50 AU/mL at 28 days following a priming dose of the ChAdOx1 nCoV-19 vaccine. In addition, solicited and unsolicited adverse events among patients with different categories of nutritional status were compared.

2.7. Statistical analyses

Categorical data are expressed as a number and percentage and were compared by using a chi-square test and Bonferroni post hoc test. Continuous data with or without a normal distribution are expressed as the means ± standard deviations or medians (interquartile ranges [IQRs]) and were compared by one-way ANOVA or the Kruskal–Wallis test, followed by Tukey's and Dunn's post-hoc tests, respectively. Logistic regression models were used in both univariate and multivariate analyses. Adjusted odds ratios (ORs) with associated 95% confidence intervals (CIs) were calculated for different degrees of malnutrition using normal nutrition as the reference. Age, sex, diabetes, CAD, cancer, and use of immunosuppressants were adjusted in the multivariate models. Bonferroni correction was applied for multiple testing and a two-tailed P value < 0.025 (0.025 = 0.05/2 tests) was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences software, version 20.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline characteristics

After the exclusion criteria were applied, a total of 206 patients (104 men and 102 women) were included in the final analysis (Fig. 1). The mean age was 66.9 ± 12.5 years and the median (IQR) dialysis vintage was 7.8 (3.3–12.5) years. Among the participants, 112 (54.4%) had diabetes, 52 (25.2%) had CAD, and 24 (11.7%) had a history of malignancy. The median (IQR) CONUT score was 3 (2–4), with 40 (19.4%) patients having a normal nutritional status, 132 (64.1%) being at risk of malnutrition, and 32 (16.5%) being malnourished. Baseline characteristics by nutritional status according to the CONUT score are presented in Table 1. Patients with malnutrition were older, were more likely to have anemia, had lower BMI, and had higher plasma glucose concentrations. As expected, serum albumin, total cholesterol, low-density lipoprotein cholesterol, triglycerides, and total lymphocyte count were lower in the malnourished group. Other characteristics that have been reported to be predictive of immunogenicity of COVID-19 vaccines, such as dialysis vintage and use of immunosuppressants [10], did not differ among the three groups.

3.2. CONUT score and immunogenicity

Overall, 138 (67.0%) patients developed a positive antibody response (≥50 AU/mL) against the SARS-CoV-2 spike protein at 28 days. Anti-spike IgG levels decreased progressively with worsening nutritional status. The median antibody levels for patients having a normal nutritional status, being at risk for malnutrition, and being malnourished were 291.0 AU/mL, 167.7 AU/mL, and 25.8 AU/mL, respectively (P = 0.004) (Table 2) (Fig. 2A). The distribution of vaccine-induced neutralizing antibodies across CONUT score groups followed a similar pattern as that seen in anti-spike antibody responses (Fig. 2B).

3.3. Primary outcome

The proportion of patients with seroconversion decreased with increasing CONUT score (P < 0.001) (Fig. 3). A lower proportion of seroconversion after vaccination was found in patients with malnutrition (41.2%) than in patients at risk for malnutrition (68.9%) or with a normal nutritional status (82.5%) (P = 0.004) (Table 2). We found that poorer nutritional status was associated with decreased odds of mounting a positive antibody response in univariate (P for trend <0.001) and multivariate logistic regression analyses (P for trend = 0.014) (Table 3). In univariate analyses, patients with malnutrition had a significantly lower chance of developing anti-spike IgG antibodies than those with a normal nutritional status (OR 0.15, 95% CI 0.05–0.43). Malnutrition remained associated with a lower chance of developing an antibody response in multivariate analyses (OR 0.23, 95% CI 0.07–0.76). The results were consistent when the CONUT score was analyzed as a continuous variable in univariate (OR 0.64, 95% CI 0.52–0.78) and multivariate analyses (OR 0.68, 95% CI 0.54–0.85).

3.4. SGA and immunogenicity

A total of 205 patients underwent SGA evaluations. Overall, 73.7% of patients were classified as in the normal nutritional group, 21.0% were classified in the moderate malnutrition group, and 5.4% were classified in the severe malnutrition group (Supplemental Table 2). Patients with a more severe degree of malnutrition were older, more likely to be female, and more likely to have a smoking history, higher urea clearance, lower BMI, and lower serum albumin. There was no difference in lipid profiles or total lymphocyte count among the groups.

A similar trend of decreasing anti-spike IgG levels with deteriorating nutritional status was observed, but it did not reach statistical significance (Supplemental Table 3). In univariate analysis, more advanced malnutrition was associated with decreased odds of antibody positivity (P = 0.013), although the association became nonsignificant when adjustments were made for potential confounders (Table 4).

3.5. Reactogenicity and safety outcomes

Solicited local and systemic reactions were similar among the 3 CONUT categories (Table 5). ChAdOx1 nCoV-19 vaccines were well tolerated in hemodialysis patients with malnutrition. No severe adverse events were observed during the 28-day observation period.

4. Discussion

In this prospective cohort study of patients undergoing hemodialysis, we found that malnutrition, either defined by CONUT or SGA, was associated with lower odds of anti-spike IgG antibody positivity following one dose of the ChAdOx1 nCoV-19 vaccine. Lower odds of seroconversion associated with malnutrition based on the CONUT score persisted even after adjustment for other potential confounders. In addition, ChAdOx1 nCoV-19 vaccines were safe and well tolerated in malnourished hemodialysis patients. The

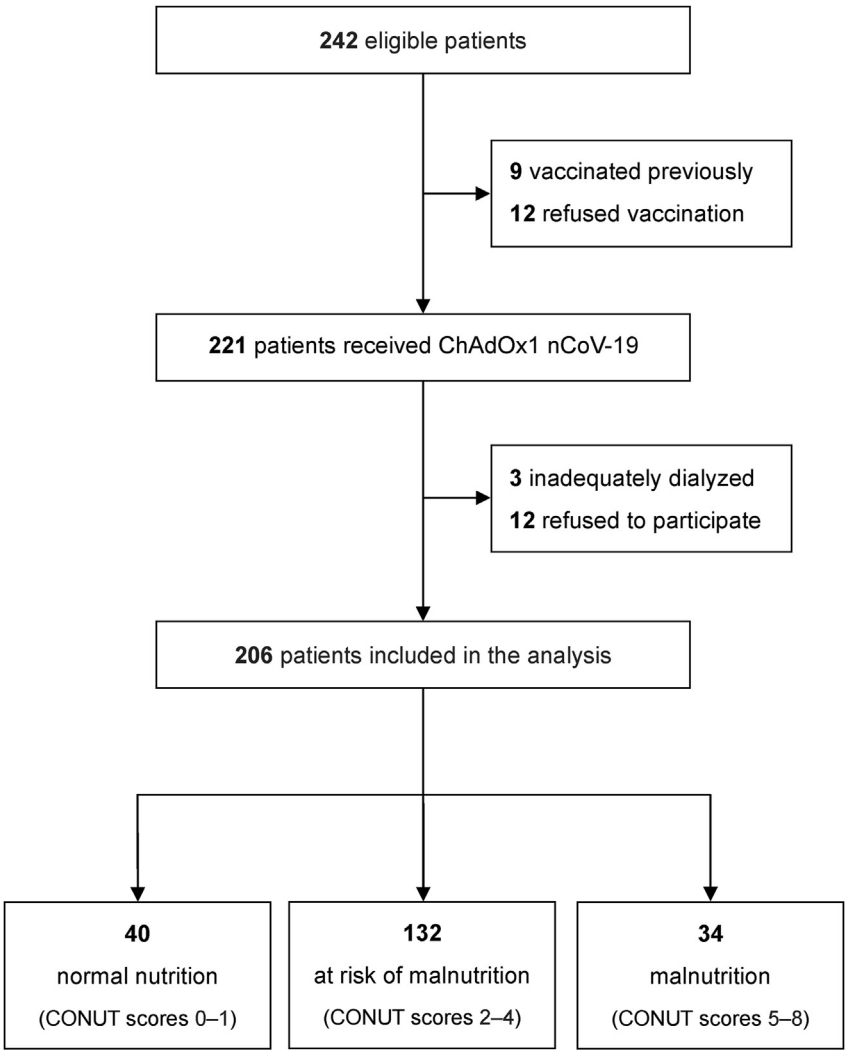

Fig. 1. Patient flow diagram.

graded association between poor nutritional status according to CONUT score and anti-spike IgG seroconversion demonstrated herein has significant implications, highlighting the importance of nutritional assessment to identify patients at risk for suboptimal immune responses after COVID-19 vaccination.

An effective immune response requires an adequate host nutritional status. Optimal nutrition provides building blocks for the generation of RNA and DNA and for the production of proteins and offers specific substrates for the production of immune-active metabolites [22]. Moreover, several vitamins and trace elements contribute to the normal functions of the immune system [23]. Consistently, a significant relationship between the number of CD3 T lymphocytes and zinc, selenium and iron as well as between CD4 T lymphocytes and zinc and selenium has been observed in dialysis patients [24]. The results from randomized controlled trials also support a cause-and-effect relationship between micronutrient status and responses to vaccination [25–27]. Broome et al. demonstrated that selenium supplementation augmented cellular responses to the live attenuated polio vaccine in healthy adults with marginal selenium status [25]. Meydani et al. reported that healthy individuals 65 years or older supplemented with 200 mg/day vitamin E had more robust cellular and humoral responses to hepatitis B and tetanus vaccines [26]. Another study of 725 institutionalized elderly patients showed that low-dose supplementation with zinc and selenium resulted in significant improvement in humoral responses after influenza vaccination [27]. Malnutrition and immune derangement are both common in patients receiving long-term dialysis [8,28]. To our knowledge, this is the first study to comprehensively assess nutritional status and demonstrate that it predicts immune responses after COVID-19 vaccination in hemodialysis patients.

Despite the expected overlap between CONUT and SGA, approximately 80% of patients were either malnourished or at risk of malnutrition according to the CONUT score, while only 26% of patients were malnourished based on the SGA. The results were consistent with a previous study investigating the agreement and classification performance of 6 nutritional assessment tools (CONUT, Geriatric Nutritional Risk Index, Prognostic Nutritional Index, Malnutrition Universal Screening Tool, Mini Nutritional Assessment–Short Form, and SGA) in patients with heart failure [29]. In this study, the CONUT score was found to have higher sensitivity, whereas SGA had better specificity in identifying at least moderate malnutrition as defined by the standard combined index. In addition, Sum et al. demonstrated that the SGA may miss 21.4% of hemodialysis patients with malnutrition when nutritional evaluations conducted by registered dietitians were considered the gold

Table 1
Baseline characteristics of hemodialysis patients according to nutritional status defined by CONUT score.

Variables	CONUT score			*P*
	Normal (0–1) ($n = 40$)	At risk (2–4) ($n = 132$)	Malnutrition (5–8) ($n = 34$)	
Demographic data				
Age (yr)	66.1 ± 11.2	65.7 ± 12.6	72.2 ± 12.6[a]	0.023
Male sex, *n* (%)	15 (37.5%)	70 (53.0%)	19 (55.9%)	0.179
Smoking history, *n* (%)	8 (20.0%)	23 (17.4%)	8 (23.5%)	0.707
Dialysis vintage (yr)	6.4 (3.2–11.2)	7.7 (3.3–12.1)	10.9 (3.6–14.6)	0.176
Kt/V	1.7 ± 0.2	1.7 ± 0.3	1.7 ± 0.2	0.843
URR (%)	76.0 ± 4.3	75.7 ± 5.8	76.5 ± 5.1	0.748
nPCR (g/kg/day)	1.13 (0.92–1.30)	1.07 (0.93–1.22)	1.07 (0.88–1.21)	0.730
BMI (kg/m^2)	24.5 ± 3.9	23.5 ± 3.9	21.7 ± 3.3[a,b]	0.007
Diabetes mellitus, *n* (%)	21 (52.5%)	68 (51.5%)	23 (67.6%)	0.234
Hypertension, *n* (%)	36 (90.0%)	118 (89.4%)	32 (94.1%)	0.707
CAD, *n* (%)	8 (20.0%)	32 (24.2%)	12 (35.3%)	0.290
Stroke, *n* (%)	2 (5.0%)	5 (3.8%)	1 (2.9%)	0.897
Cancer, *n* (%)	4 (10.0%)	12 (9.1%)	8 (23.5%)	0.061
Use of IS, *n* (%)	0 (0.0%)	5 (3.8%)	0 (0.0%)	0.238
Laboratory data				
Albumin (g/dl)	3.9 (3.7–4.0)	3.9 (3.7–4.0)	3.5 (3.3–3.9)[a,b]	0.001
Fasting glucose (mg/dl)	125 (100–170)	140 (117–194)	166 (130–218)[b]	0.009
Total cholesterol (mg/dl)	190 (164–217)	154 (128–174)[c]	128 (112–136)[a,b]	<0.001
Triglycerides (mg/dl)	186 (127–243)	138 (95–198)[c]	113 (86–141)[a,b]	<0.001
LDL (mg/dl)	105 (90–118)	79 (61–97)[c]	59 (51–69)[a,b]	<0.001
Lymphocyte ($x10^9/l$)	1.7 (1.4–2.0)	1.1 (0.9–1.3)[c]	0.7 (0.6–1.0)[a,b]	<0.001
Hemoglobin (g/dl)	10.5 (9.8–11.2)	10.5 (9.6–11.0)	9.6 (9.2–10.5)[b]	0.017
Ferritin (ng/ml)	409 (114–580)	480 (276–629)	525 (285–718)	0.110
Calcium (mg/dl)	9.5 (8.9–10.0)	9.4 (8.9–10.1)	9.4 (8.8–9.9)	0.839
Phosphate (mg/dl)	4.4 (3.5–5.5)	4.5 (3.6–5.3)	4.2 (3.7–5.2)	0.881
iPTH (pg/ml)	237 (102–650)	332 (140–587)	405 (219–634)	0.243

BMI, body mass index; CAD, coronary artery disease; CONUT, Controlling Nutritional Status; iPTH, intact parathyroid hormone; IS, immunosuppressant; LDL, low-density lipoprotein; nPCR, normalized protein catabolic rate; URR, urea reduction ratio.
[a] At risk of malnutrition and malnutrition are significantly different, $P < 0.05$.
[b] Normal nurition and malnutrition are significantly different, $P < 0.05$.
[c] Normal nurition and risk of malnutrition are significantly different, $P < 0.05$.

Table 2
Humoral immune response according to nutritional status defined by CONUT score.

Variables	CONUT score			*P*
	Normal (0–1) ($n = 40$)	At risk (2–4) ($n = 132$)	Malnutrition (5–8) ($n = 34$)	
Anti-spike antibody titer range				
<50 AU/ml	7 (17.5%)	41 (31.1%)	20 (58.8%)[a,b]	0.004
≥50 AU/ml	33 (82.5%)	91 (68.9%)	14 (41.2%)	
Anti-spike antibody (AU/ml)	291.0 (110.9–619.6)	167.7 (14.8–538.1)	25.8 (0.0–269.6)[a,b]	0.004
Neutralizing antibody (NT_{50})	2.18 (1.28–4.15)	1.43 (0.95–2.99)	1.11 (0.86–1.67)[a,b]	0.001

AU, arbitrary unit; CONUT, Controlling Nutritional Status; NT_{50}, 50% neutralizing titer.
[a] At risk of malnutrition and malnutrition are significantly different, $P < 0.05$.
[b] Normal nurition and malnutrition are significantly different, $P < 0.05$.

standard [30]. Indeed, the SGA was able to differentiate severely malnourished patients from those with a normal nutritional status, but appeared not to be a reliable predictor of the degree of malnutrition [31]. A lack of an independent association between SGA and anti-spike IgG seroconversion in the present study can be explained in part by the very low percentage of severe malnutrition identified by SGA.

In our study, the CONUT score independently predicted humoral responses to COVID-19 vaccines. CONUT evaluates nutritional status from various perspectives using 3 biomarkers: serum albumin, total cholesterol, and total lymphocyte count. While albumin and cholesterol may more reflect the individual's protein and lipid reserve [9], activation of the immune response requires the availability of fatty acids and amino acids for the production of lipid-derived mediators such as prostaglandins and many different types of proteins such as immunoglobulins and cytokines [23]. It is also not surprising that lymphocytes play a role in the immune system in general and the production of antibodies in particular [32]. Malnutrition has been proposed as the most common cause of secondary immune dysfunction [33]. Failure to recognize the development of malnutrition and intervene appropriately could have fatal consequences in dialysis patients [9]. Although the 2020 KDOQI Clinical Practice Guideline for Nutrition recommended the use of SGA to assess nutritional status in chronic kidney disease, one of the important highlights of the updated guidelines is the recognition of a poor level of evidence to use one tool over others for the diagnosis of malnutrition [12]. The CONUT score can be calculated quickly from a routine blood examination. Based on our results, COUNT is a useful tool for the identification of malnourished dialysis patients who are at risk of decreased vaccine effectiveness against SARS-CoV-2 infection.

Our study raises the question of whether nutritional supplementation should be recommended in malnourished hemodialysis patients to optimize the COVID-19 vaccination response. Although there has been no direct evidence relating an improved immune response with the provision of nutritional supplements in dialysis

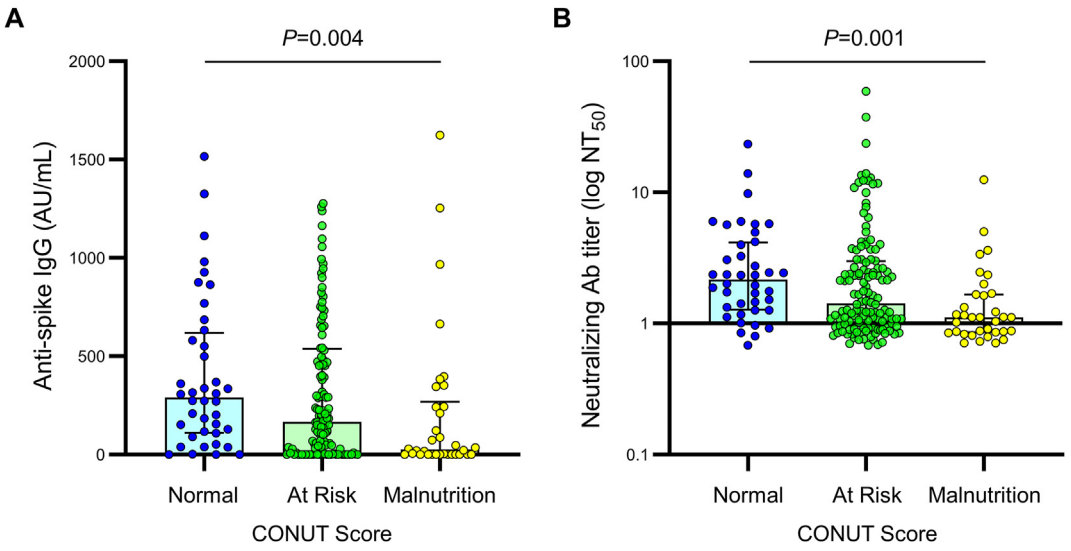

Fig. 2. (A) SARS-CoV-2 anti-spike antibody concentrations, and (B) SARS-CoV-2 neutralizing antibody titers at 28 days following the first dose of the ChAdOx1 nCoV-19 vaccine by nutritional status according to the CONUT score. The median and IQR are shown. AU, arbitrary unit; NT_{50}, 50% neutralizing titer.

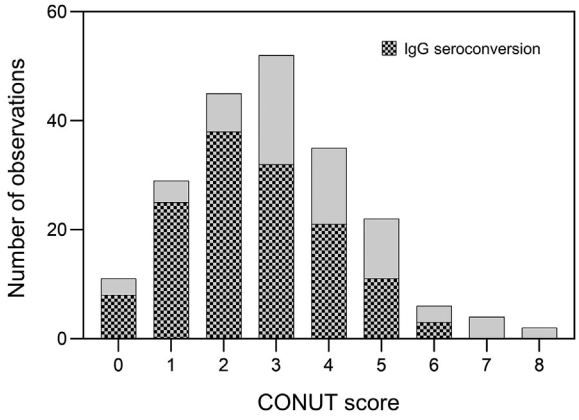

Fig. 3. Proportions of patients achieving SARS-CoV-2 anti-spike antibody seroconversion according to the CONUT socre. CONUT, controlling nutritional status.

Table 3
Humoral response to SARS-CoV-2 vaccination at the 4th week after vaccination according to nutritional status defined by CONUT score.

Variables	Unadjusted	Multivariate
	Odds ratio (95% CI)	Odds ratio (95% CI)
CONUT, categorical		
Normal	Reference	Reference
At risk	0.47 (0.19–1.15)	0.53 (0.20–1.44)
Malnutrition	0.15 (0.05–0.43)	0.23 (0.07–0.76)
P for trend	<0.001	0.014
CONUT, continuous		
Per 1-point increment	0.64 (0.52–0.78)	0.68 (0.54–0.85)

CONUT, controlling nutritional status.
Multivariate: adjusted for age, sex, diabetes, coronary artery disease, cancer, and use of immunosuppressants.

Table 4
Humoral response to SARS-CoV-2 vaccination at the 4th week after vaccination according to nutritional status defined by SGA.

Variables	Unadjusted	Multivariate
	Odds ratio (95% CI)	Odds ratio (95% CI)
SGA, categorical		
Normal	Reference	Reference
Moderate malnutrition	0.61 (0.30–1.23)	0.98 (0.41–2.30)
Severe malnutrition	0.23 (0.06–0.82)	0.43 (0.10–1.89)
P for trend	0.013	0.399
SGA, continuous		
Per 1-point increment	1.43 (1.12–1.82)	1.18 (0.87–1.59)

SGA, subjective global assessment.
Multivariate: adjusted for age, sex, diabetes, coronary artery disease, cancer, and use of immunosuppressants.

patients, several studies have revealed malnutrition to be a potentially modifiable risk factor and therapeutic target [34]. In a randomized controlled trial, hemodialysis patients with insufficient intake have shown the capacity to respond to a renal-specific oral supplement, with changes in serum albumin and prealbumin positively correlated with the increment in protein intake, resulting in improved SGA [35]. A multicenter randomized controlled trial of 186 malnourished patients receiving oral nutritional supplements with or without 1 year of intradialytic parenteral nutrition reported that both groups exhibited a similar improvement in nutritional status as measured by BMI and serum albumin [36]. Given the evidence available at the moment, nutritional support may be considered in malnourished hemodialysis patients before COVID-19 vaccination.

Apart from the poor immune response following vaccination, malnutrition is also associated with adverse COVID-19 outcomes. Abate et al. performed a systematic review and meta-analysis to examine the impact of malnutrition on hospitalized COVID-19 patients [37]. Among the 14 articles with 4187 participants included, they found that the pooled prevalence of malnutrition was 49.11% (95% CI 31.67–66.54), and the odd of mortality among patients with malnutrition was 10 times more likely as compared to those who were well-nourished. Thus, attention should be focused on preventing and managing malnutrition and its outcomes in the COVID-19 pandemic.

Our study has several limitations that need to be acknowledged. First, seroconversions of anti-spike IgG antibody do not necessarily equate to protection against infection. To date, there have been no defined correlates of protection against SARS-CoV-2 infection, and longitudinal clinical follow-up will be required to validate the positive effects of nutrition on COVID-19–related complications.

Table 5
Frequency of local and systemic solicited side effects according to nutritional status.

Variables	CONUT score			*P*
	Normal (0–1) ($n = 40$)	At risk (2–4) ($n = 132$)	Malnutrition (5–8) ($n = 34$)	
Local reaction, *n* (%)	17 (42.5%)	47 (35.6%)	16 (47.1%)	0.412
Pain, *n* (%)	16 (40.0%)	45 (34.1%)	16 (47.1%)	0.352
Redness, *n* (%)	4 (10.0%)	11 (8.3%)	4 (11.8%)	0.812
Swelling, *n* (%)	6 (15.0%)	14 (10.6%)	5 (14.7%)	0.668
Systemic reaction, *n* (%)	24 (60.0%)	81 (61.4%)	14 (41.2%)	0.099
Fever, *n* (%)	11 (27.5%)	41 (31.1%)	8 (23.5%)	0.668
Headache, *n* (%)	6 (15.0%)	22 (16.7%)	6 (17.6%)	0.951
Muscle and joint pain, *n* (%)	11 (27.5%)	31 (23.5%)	5 (14.7%)	0.406
Nausea or vomiting, *n* (%)	1 (2.5%)	2 (1.5%)	1 (2.9%)	0.831
Abdominal pain, *n* (%)	1 (2.5%)	7 (5.3%)	3 (8.8%)	0.483
Diarrhea, *n* (%)	4 (10.0%)	7 (5.3%)	3 (8.8%)	0.513
Fatigue, *n* (%)	8 (20.0%)	45 (34.1%)	9 (26.5%)	0.207
Rash, *n* (%)	1 (2.5%)	2 (1.5%)	0 (0.0%)	0.667
Any symptom, *n* (%)	29 (72.5%)	89 (67.4%)	20 (58.8%)	0.453

CONUT, controlling nutritional status.

Second, the association between nutritional status and cellular responses was not assessed. Nevertheless, a moderate correlation between humoral and cellular responses after administration of the BNT162b2 mRNA vaccine has been demonstrated in patients on hemodialysis [38]. Third, we assessed the serological response at 28 days alone following vaccination. However, prior studies have identified an incomplete and delayed humoral response to SARS-CoV-2 vaccination in hemodialysis patients [10]. Finally, our results are from hemodialysis patients who received an adenovirus-vectored vaccine. The impact of malnutrition on immune responses to other vaccines against SARS-CoV-2 might be different, which limits the generalizability of our findings.

5. Conclusion

In conclusion, immune responses to COVID-19 vaccination are significantly impaired in patients treated with hemodialysis classified as malnourished according to CONUT score. Earlier or additional booster vaccination and strict adherence to non-pharmacological interventions may be particularly advantageous for this population. Improving nutritional status, on the other hand, could emerge as a practical means to help optimize vaccination response. Further research is needed to determine whether malnourished hemodialysis patients would benefit from nutritional interventions before COVID-19 vaccination.

Statement of Authorship

All authors contributed significantly. TYL, NKH, and SCH contributed to the acquisition, analysis or interpretation of data for the work, and drafted the manuscript. TYL and SCH contributed to study design and method, and critically revised the manuscript. TYL helped with the statistical analyses. Each author are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final version of this manuscript.

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Conflict of Interest

All authors have declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.10.011.

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