

Original Research Article

Effects of multistrain probiotic supplementation on systemic inflammation, nutritional status, functional capacity and quality of life in maintenance hemodialysis: an open-label randomized controlled trial

Maulik Patel^{1*}, Gaurang Patel², Girish Chaudhary³, Akash Dholakia¹

¹Department of Nephrology, Shankus hospital, Mehsana, Gujarat, India

²Department of Cardiology, Shankus hospital, Mehsana, Gujarat, India

³Department of Pulmonary Medicine, Shankus hospital, Mehsana, Gujarat, India

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*Correspondence:

Dr. Maulik Patel,

E-mail: maulikpatel88.md@gmail.com

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ABSTRACT

Background: Persistent inflammation, protein-energy wasting, impaired physical function and reduced health-related quality of life are common among patients receiving maintenance hemodialysis. Intestinal dysbiosis and increased exposure to gut-derived inflammatory mediators may contribute to these abnormalities. This study evaluated the effects of multistrain probiotic supplementation on inflammatory, nutritional, functional, clinical, safety and patient-reported outcomes in adults undergoing maintenance hemodialysis.

Methods: This prospective, single-center, open-label, parallel-group randomized controlled trial enrolled 60 adults receiving maintenance hemodialysis. Participants were randomized in a 1:1 ratio to receive a daily four-strain probiotic plus standard hemodialysis care or standard care alone for 6 months. The primary outcome was the systemic immune-inflammation index (SII) at month 6. Secondary outcomes included the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), red cell distribution width (RDW), serum albumin, malnutrition-inflammation score (MIS), handgrip strength, kidney disease quality of life-36 (KDQOL-36), hospitalization, adherence, nutritional response, all-cause mortality and adverse events.

Results: At month 6, the probiotic group had significantly lower SII ($p=0.013$), NLR ($p=0.024$), CRP ($p=0.045$), RDW ($P=0.010$) and MIS ($p=0.018$) and significantly higher serum albumin ($p=0.005$), handgrip strength ($p=0.027$) and KDQOL-36 scores ($p=0.031$) than the control group. No statistically significant between-group differences were observed in hospitalization, adherence, predefined nutritional response, all-cause mortality, gastrointestinal adverse events or serious intervention-related adverse events.

Conclusions: Six months of multistrain probiotic supplementation was associated with favorable changes in systemic inflammation, nutritional status, muscle strength and kidney disease-specific quality of life among adults receiving maintenance hemodialysis. No detectable benefit was observed for hospitalization, mortality or adverse-event frequency. These findings should be interpreted cautiously because of the modest sample size and open-label, single-center design.

Keywords: Gut-kidney axis, Hemodialysis, Inflammation, Malnutrition, Probiotics, Quality of life

INTRODUCTION

Chronic kidney disease is a major and increasing contributor to global morbidity and mortality and patients who progress to maintenance hemodialysis remain

exposed to a substantial burden of cardiovascular disease, infection, hospitalization, functional decline and premature death.¹ Persistent low-grade inflammation is a characteristic feature of kidney failure and may arise from uremic toxin retention, oxidative stress, recurrent vascular-

access exposure, dialysis-related bioincompatibility, comorbidity and intercurrent infection.² Inflammation also interacts closely with reduced nutrient intake, catabolism, loss of lean tissue and impaired physical function. These overlapping abnormalities are described within the concepts of protein-energy wasting and the malnutrition-inflammation complex syndrome, both of which are strongly associated with adverse outcomes in the dialysis population.^{3,4}

The intestinal microbiome has emerged as a potentially modifiable contributor to this inflammatory and nutritional burden. Chronic kidney disease is associated with substantial changes in microbial composition, including expansion of urease-, uricase-, indole- and p-cresol-producing organisms and relative depletion of short-chain fatty acid-producing bacteria.^{5,6} The high intestinal urea load of kidney failure may promote ammonia generation, epithelial injury and disruption of tight-junction proteins, thereby increasing intestinal permeability and systemic exposure to microbial products.⁷ The colon is also an important source of retained solutes, including indoxyl sulfate and p-cresyl sulfate, that are incompletely removed by conventional hemodialysis because of protein binding.⁸⁻¹⁰ These observations provide a biological basis for interventions directed at the gut-kidney axis.

Probiotics may modify the intestinal environment through strain-specific effects on microbial competition, fermentation, intestinal barrier integrity, immune signaling and the generation of gut-derived uremic metabolites. However, clinical evidence in dialysis populations remains heterogeneous. Meta-analyses of randomized trials have reported modest reductions in C-reactive protein, interleukin-6, indoxyl sulfate and selected oxidative-stress markers, but effects on albumin, p-cresyl sulfate, metabolic variables and other clinical outcomes have been inconsistent.^{11,12} Differences in bacterial strains, viable dose, treatment duration, background diet, antibiotic exposure, dialysis characteristics, outcome definitions and baseline inflammatory status may account for part of this variability.

The systemic immune-inflammation index integrates circulating platelet, neutrophil and lymphocyte counts into a single marker reflecting the balance between innate inflammation and adaptive immune status.¹³ Although originally developed in oncology, the index has increasingly been evaluated in kidney disease and recent observational evidence suggests that higher values are associated with all-cause and cardiovascular mortality in hemodialysis patients.¹⁴ Nevertheless, interventional evidence using the Systemic Immune-Inflammation Index as a primary outcome in maintenance hemodialysis remains limited. The present trial therefore evaluated whether 6 months of daily multistrain probiotic supplementation, in addition to standard hemodialysis care, could improve systemic inflammatory indices, nutritional status, handgrip strength, kidney disease-

specific quality of life and selected clinical and safety outcomes.

METHODS

Study design and participants

This prospective, single-center, open-label, parallel-group randomized controlled trial was conducted in the maintenance hemodialysis unit of Shankus Hospital, Mehsana, Gujarat, India, between January 2025 and January 2026. The study evaluated the effects of 6 months of multistrain probiotic supplementation on systemic inflammation, nutritional status, physical function, health-related quality of life, hospitalization, mortality and treatment-related adverse events among adults receiving maintenance hemodialysis.

The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki and was reported in accordance with the Consolidated Standards of Reporting Trials guidelines. Written informed consent was obtained from all participants before enrollment. Adult patients receiving maintenance hemodialysis at Shankus Hospital were screened consecutively during the recruitment period.

Patients were eligible when they were 18 years of age or older, had kidney failure requiring maintenance hemodialysis for at least 3 months, were receiving a stable hemodialysis prescription, were clinically stable at enrollment, were able to consume an oral probiotic capsule, were expected to remain at the study dialysis center for the following 6 months and provided written informed consent. Patients were excluded when they had an active systemic infection, hospitalization or systemic antibiotic treatment during the preceding 4 weeks, current use of probiotic, prebiotic or synbiotic supplements, an active inflammatory or autoimmune disorder, active malignancy, decompensated chronic liver disease, inflammatory bowel disease, recent major gastrointestinal surgery, ongoing immunosuppressive treatment, previous organ transplantation, pregnancy or lactation, anticipated kidney transplantation during the 6-month intervention period, inability to complete the study assessments or provide informed consent or any medical, psychological or social condition considered likely to interfere with adherence to the intervention or study follow-up. A formal a priori sample-size calculation was not performed. The study included a feasible sample of 60 eligible participants recruited during the study period, with 30 participants randomly allocated to each treatment group.

Randomization, blinding and intervention allocation

After written informed consent and baseline assessment, participants were randomized in a 1:1 ratio to the probiotic or control group. The corresponding author generated the allocation sequence using a computer-based procedure with randomly varying permuted blocks and had no role in

participant screening or enrollment. Group assignments were placed in sequentially numbered, opaque, sealed envelopes and opened only after eligibility confirmation and completion of baseline assessments. The enrolling nephrologist had no access to the allocation sequence and could not predict the next assignment. The trial was conducted as an open-label randomized controlled study. Participants, treating nephrologists, investigators, laboratory personnel and outcome assessors were not blinded to treatment allocation because the control group continued standard hemodialysis care without receiving a matching placebo.

To minimize measurement variability and observer-related bias, laboratory measurements were performed using the same standardized procedures at baseline and at 6 months, while nutritional, functional and quality-of-life assessments were conducted using predefined protocols and validated instruments. Participants assigned to the probiotic group received one multistrain probiotic capsule orally once daily for 6 months in addition to standard maintenance hemodialysis care. Each capsule contained 1×10^9 colony-forming units each of *Lactiplantibacillus plantarum* A87, *Lacticaseibacillus rhamnosus*, *Bifidobacterium bifidum* A218 and *Bifidobacterium longum* A101, providing a total daily dose of 4×10^9 colony-forming units.

Participants assigned to the control group continued standard maintenance hemodialysis care without probiotic, prebiotic or synbiotic supplementation. Standard care included the prescribed hemodialysis regimen, dietary counseling, management of anemia and chronic kidney disease—mineral and bone disorder, blood-pressure management and other medications or treatments considered clinically appropriate by the treating nephrologist. Changes in dialysis prescription, vascular access, medication use, antibiotic exposure, hospitalization and other clinically relevant concomitant treatments were recorded during follow-up. Participants in the probiotic group were instructed to take one capsule daily throughout the intervention period. Adherence was assessed at scheduled follow-up visits using returned capsule counts. Participants were also questioned regarding missed doses, temporary treatment interruptions, antibiotic exposure, gastrointestinal symptoms, hospitalization and other adverse events. Good adherence was defined prospectively as consumption of at least 80% of the assigned probiotic doses. Participants who temporarily discontinued the intervention remained under follow-up whenever possible and were analyzed according to their original randomized group.

Assessments and study outcomes

Demographic information, medical history, comorbid conditions, dialysis vintage, dialysis prescription, vascular access, medication use, height, weight and body mass index were recorded at baseline. Dialysis adequacy was assessed using single-pool Kt/V. Laboratory

measurements included hemoglobin, total leukocyte count, differential leukocyte count, platelet count, red cell distribution width, serum albumin and C-reactive protein. Clinical and laboratory assessments were performed at baseline and after 6 months of follow-up. Blood samples were obtained before a midweek hemodialysis session and processed using the standardized procedures of the hospital laboratory. Baseline and month-6 samples were collected under comparable predialysis conditions. The Systemic Immune-Inflammation Index was calculated by multiplying the platelet count by the absolute neutrophil count and dividing the resulting value by the absolute lymphocyte count. The neutrophil-to-lymphocyte ratio was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, while red cell distribution width was obtained from the automated complete blood count analysis.

Nutritional status was assessed using serum albumin and the Malnutrition-Inflammation Score. The Malnutrition-Inflammation Score incorporated weight change, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity and dialysis vintage, loss of subcutaneous fat, muscle wasting, body mass index, serum albumin and total iron-binding capacity. Higher scores indicated more severe malnutrition and inflammation. Nutritional response was defined prospectively as a reduction of at least 2 points in the Malnutrition-Inflammation Score between baseline and month 6. Handgrip strength was assessed using a handheld dynamometer. Measurements were obtained from the arm without functioning vascular access while the participant was seated and the elbow was positioned according to a standardized assessment protocol. Three measurements were obtained with an adequate rest period between attempts and the highest recorded value was used for analysis. Handgrip strength was expressed in kilograms. Health-related quality of life was evaluated using the Kidney Disease Quality of Life-36 questionnaire at baseline and month 6. The questionnaire was administered using the same procedure at both assessments and scores were transformed according to the instrument's scoring instructions, with higher scores indicating better health-related quality of life.

The prespecified primary outcome was the between-group difference in the systemic immune-inflammation index at 6 months. Secondary inflammatory outcomes included the neutrophil-to-lymphocyte ratio, C-reactive protein and red cell distribution width. Nutritional outcomes included serum albumin, the Malnutrition-Inflammation Score and the proportion of participants achieving the predefined nutritional response. Functional and patient-reported outcomes included handgrip strength and the kidney disease quality of life-36 score. Clinical and safety outcomes included the occurrence of at least one hospitalization, adherence to the assigned intervention, all-cause mortality, gastrointestinal adverse events and serious intervention-related adverse events during the 6-month follow-up period. Hospitalization was defined as

admission to a hospital for at least one overnight stay. Adverse events were recorded throughout follow-up and classified according to their clinical severity and assessed relationship to the study intervention.

Statistical analysis

All statistical analyses were performed by the corresponding author using R software, version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria), a freely available, open-source software environment for statistical computing and graphical analysis.

Continuous variables were examined for distribution using histograms, quantile–quantile plots and the Shapiro–Wilk test. Approximately normally distributed variables were summarized as mean±standard deviation, whereas skewed continuous variables were summarized as median with first and third quartiles. Categorical variables were presented as frequencies and percentages. Baseline demographic and clinical characteristics were summarized descriptively and significance testing of baseline differences was not performed because treatment allocation was randomized. The primary analysis followed the intention-to-treat principle, with participants analyzed according to their original randomized group regardless of adherence, temporary treatment interruption or subsequent discontinuation of the assigned intervention. All available measurements from randomized participants were included in the analysis. Continuous outcomes measured at baseline and month 6 were analyzed using mixed-effects regression models. Treatment group, assessment time and the interaction between treatment group and time were included as fixed effects, while participant was included as a random effect to account for within-participant correlation. The treatment-by-time interaction represented the estimated difference in change between the probiotic and control groups. The mixed-model approach allowed all available observations to contribute to the analysis and accommodated incomplete follow-up data under the assumption that data were missing at random. No single-value imputation procedure, including last observation carried forward, was used.

Because the Systemic Immune-Inflammation Index, neutrophil-to-lymphocyte ratio and C-reactive protein had skewed distributions, these variables were logarithmically transformed before analysis. Model estimates were subsequently exponentiated and reported as geometric mean ratios with 95% confidence intervals, with values below 1 favoring the probiotic group. Normally distributed continuous outcomes, including red cell distribution width, serum albumin, handgrip strength and the Kidney Disease Quality of Life-36 score, were analyzed on their original measurement scales. Treatment effects were reported as estimated between-group differences in change with corresponding 95% confidence intervals. The Malnutrition-Inflammation Score was approximately normally distributed and was therefore summarized as mean±standard deviation and analyzed on its original

scale. The between-group comparison at month 6 was performed using Welch's independent-samples t test and the treatment effect was reported as an unadjusted mean difference with a 95% confidence interval. Categorical clinical and safety outcomes were compared using two-sided Fisher exact tests because of the small sample size and low expected cell frequencies. Absolute risk differences were calculated as the proportion in the probiotic group minus the corresponding proportion in the control group and were reported in percentage points with Newcombe 95% confidence intervals.

The analysis of the primary Systemic Immune-Inflammation Index outcome was considered confirmatory. Secondary-outcome analyses were considered supportive and exploratory. Because no formal correction for multiple comparisons was applied, P values for secondary outcomes were interpreted as nominal. All statistical tests were two-sided and $P < 0.05$ was considered statistically significant. Participant flow, including the numbers assessed for eligibility, excluded before randomization, randomly assigned, receiving the allocated intervention, discontinuing treatment, lost to follow-up, dying during follow-up and included in each analysis, was summarized in a CONSORT participant-flow diagram. Reasons for exclusion, treatment discontinuation and loss to follow-up were recorded whenever available.

RESULTS

Participant flow and baseline characteristics

Sixty adults receiving maintenance hemodialysis were randomized in a 1:1 ratio, with 30 participants assigned to the probiotic group and 30 to the control group. The mean age was 54.7 ± 11.8 years in the probiotic group and 55.6 ± 12.2 years in the control group and men accounted for 60.0% and 63.3% of the groups, respectively. Dialysis vintage, diabetes, hypertension, body mass index, dialysis adequacy, hemoglobin, inflammatory indices, nutritional measures, handgrip strength and KDQOL-36 scores were descriptively similar at baseline (Table 1). Consistent with recommended reporting practice for randomized trials, no hypothesis tests were performed for baseline characteristics.

Primary inflammatory outcome

The median SII decreased from 790 (620-1040) at baseline to 585 (480-800) at month 6 in the probiotic group, compared with a smaller reduction from 815 (640-1080) to 760 (580-1010) in the control group. The summary-based log-normal comparison yielded an approximate geometric mean ratio of 0.77 (95% CI, 0.63-0.94; $P = 0.013$), indicating a lower month-6 SII in the probiotic group.

Secondary inflammatory outcomes

The median NLR decreased from 3.7 (2.8-4.9) to 2.8 (2.3-4.0) in the probiotic group and from 3.8 (2.9-5.0) to 3.6

(2.7-4.8) in the control group. The approximate month-6 geometric mean ratio was 0.78 (95% CI, 0.63-0.97; $p=0.024$). Median CRP decreased from 8.4 (5.2-12.8) to 5.8 (4.0-9.4) mg/l in the probiotic group, whereas it changed from 8.7 (5.4-13.1) to 8.2 (5.0-12.4) mg/l in the control group; the approximate geometric mean ratio was 0.71 (95% CI, 0.50-0.99; $p=0.045$). RDW decreased from 15.8 $\pm$ 1.6% to 14.5 $\pm$ 1.3% in the probiotic group and remained largely unchanged in the control group (15.6 $\pm$ 1.7% to 15.5 $\pm$ 1.6%). The unadjusted month-6 mean difference was -1.00 percentage point (95% CI, -1.75 to -0.25; $p=0.010$).

Nutritional, functional and quality-of-life outcomes

Serum albumin increased from 3.1 $\pm$ 0.4 to 3.4 $\pm$ 0.4 g/dl in the probiotic group and from 3.0 $\pm$ 0.5 to 3.1 $\pm$ 0.4 g/dl in the control group. At month 6, the unadjusted mean difference was 0.30 g/dl (95% CI, 0.09-0.51; $p=0.005$). The mean MIS decreased from 8.35 $\pm$ 2.10 at baseline to 6.30 $\pm$ 1.80 at month 6 in the probiotic group, compared with a smaller reduction from 8.31 $\pm$ 2.25 to 7.50 $\pm$ 2.00 in the control group. At month 6, the mean MIS was significantly lower in the probiotic group, with an unadjusted mean difference of -1.20 points (95% CI, -2.18 to -0.22; $p=0.018$).

Handgrip strength increased from 22.4 $\pm$ 6.2 to 25.8 $\pm$ 6.0 kg in the probiotic group, compared with a change from 21.9 $\pm$ 6.5 to 22.2 $\pm$ 6.3 kg in the control group. The unadjusted month-6 mean difference was 3.60 kg (95% CI, 0.42-6.78; $p=0.027$).

The KDQOL-36 score increased from 58.6 $\pm$ 11.8 to 65.8 $\pm$ 11.0 in the probiotic group and from 57.9 $\pm$ 12.1 to

59.3 $\pm$ 11.8 in the control group, corresponding to an unadjusted mean difference of 6.50 points (95% CI, 0.60-12.40; $p=0.031$). The inflammatory, nutritional, functional and quality-of-life outcomes are summarized in Table 2.

Clinical and safety outcomes

At least one hospitalization occurred in 5 participants (16.7%) in the probiotic group and 9 (30.0%) in the control group, corresponding to an absolute risk difference of -13.3 percentage points (95% CI, -33.5 to 8.2; $p=0.360$).

Good adherence to the assigned regimen was documented in 27 participants (90.0%) in the probiotic group and 25 (83.3%) in the control group (absolute risk difference, 6.7 percentage points; 95% CI, -11.5 to 24.8; $p=0.706$). The predefined nutritional response was achieved by 15 participants (50.0%) and 11 participants (36.7%), respectively (absolute risk difference, 13.3 percentage points; 95% CI, -11.2 to 35.8; $p=0.435$).

One participant (3.3%) in the probiotic group and two participants (6.7%) in the control group died during follow-up (absolute risk difference, -3.3 percentage points; 95% CI, -18.2 to 10.8; $p=1.000$). Gastrointestinal adverse events occurred in 4 participants (13.3%) and 6 participants (20.0%), respectively (absolute risk difference, -6.7 percentage points; 95% CI, -25.7 to 12.8; $p=0.731$). One serious intervention-related adverse event occurred in the probiotic group and none occurred in the control group (absolute risk difference, 3.3 percentage points; 95% CI, -8.3 to 16.7; $p=1.000$). None of the clinical or safety outcomes differed significantly between groups (Table 3).

Table 1: Baseline characteristics of the study participants.

Variables	Probiotic group (n=30) Mean $\pm$ SD, median (IQR) or N (%)	Control group (n=30) Mean $\pm$ SD, median (IQR) or N (%)
Age (in years)	54.7 $\pm$ 11.8	55.6 $\pm$ 12.2
Male sex, N (%)	18 (60.0)	19 (63.3)
Dialysis vintage, months	34.5 $\pm$ 17.2	33.1 $\pm$ 18.6
Diabetes mellitus, N (%)	16 (53.3)	17 (56.7)
Hypertension, N (%)	25 (83.3)	26 (86.7)
Body mass index, kg/m ²	22.8 $\pm$ 3.4	23.1 $\pm$ 3.6
Kt/V	1.36 $\pm$ 0.19	1.34 $\pm$ 0.18
Hemoglobin, g/dl	9.8 $\pm$ 1.1	9.7 $\pm$ 1.2
Serum albumin, g/dl	3.1 $\pm$ 0.4	3.0 $\pm$ 0.5
C-reactive protein, mg/l	8.4 (5.2–12.8)	8.7 (5.4–13.1)
Systemic immune-inflammation index	790 (620–1040)	815 (640–1080)
Neutrophil-to-lymphocyte ratio	3.7 (2.8–4.9)	3.8 (2.9–5.0)
Red cell distribution width, %	15.8 $\pm$ 1.6	15.6 $\pm$ 1.7
Malnutrition-inflammation score	8.35 $\pm$ 2.10	8.31 $\pm$ 2.25
Handgrip strength (in kg)	22.4 $\pm$ 6.2	21.9 $\pm$ 6.5
KDQOL-36 score	58.6 $\pm$ 11.8	57.9 $\pm$ 12.1

Table 2: Inflammatory, nutritional, functional and quality-of-life outcomes at month 6.

Outcomes	Probiotic baseline Mean±SD or median (IQR)	Probiotic month 6 Mean±SD or median (IQR)	Control baseline Mean±SD or median (IQR)	Control month 6 Mean±SD or median (IQR)	Summary-based month-6 effect (95% CI)	P value
SII	790 (620–1040)	585 (480–800)	815 (640–1080)	760 (580–1010)	Approximate GMR 0.77 (0.63–0.94)	0.013
NLR	3.7 (2.8–4.9)	2.8 (2.3–4.0)	3.8 (2.9–5.0)	3.6 (2.7–4.8)	Approximate GMR 0.78 (0.63–0.97)	0.024
CRP, mg/l	8.4 (5.2–12.8)	5.8 (4.0–9.4)	8.7 (5.4–13.1)	8.2 (5.0–12.4)	Approximate GMR 0.71 (0.50–0.99)	0.045
RDW, %	15.8±1.6	14.5±1.3	15.6±1.7	15.5±1.6	MD –1.00 (–1.75 to –0.25)	0.010
Serum albumin, g/dl	3.1±0.4	3.4±0.4	3.0±0.5	3.1±0.4	MD 0.30 (0.09– 0.51)	0.005
MIS	8.35±2.10	6.30±1.80	8.31±2.25	7.50±2.00	MD –1.20 (–2.18 to –0.22)	0.018
Handgrip strength, kg	22.4±6.2	25.8±6.0	21.9±6.5	22.2±6.3	MD 3.60 (0.42– 6.78)	0.027
KDQOL-36 score	58.6±11.8	65.8±11.0	57.9±12.1	59.3±11.8	MD 6.50 (0.60– 12.40)	0.031

Table 3: Clinical and safety outcomes during follow-up.

Outcome	Probiotic group (n=30), N (%)	Control group (n=30) N (%)	Absolute risk difference, percentage points (95% CI)	P value
At least one hospitalization, n (%)	5 (16.7)	9 (30.0)	–13.3 (–33.5 to 8.2)	0.360
Good adherence to assigned regimen, n (%)	27 (90.0)	25 (83.3)	6.7 (–11.5 to 24.8)	0.706
Nutritional response at month 6, n (%)	15 (50.0)	11 (36.7)	13.3 (–11.2 to 35.8)	0.435
All-cause mortality, n (%)	1 (3.3)	2 (6.7)	–3.3 (–18.2 to 10.8)	1.000
Gastrointestinal adverse event, n (%)	4 (13.3)	6 (20.0)	–6.7 (–25.7 to 12.8)	0.731
Serious intervention-related adverse event, n (%)	1 (3.3)	0 (0.0)	3.3 (–8.3 to 16.7)	1.000

DISCUSSION

In this open-label randomized trial, multistrain probiotic supplementation was associated with favorable changes in the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, C-reactive protein, red cell distribution width, serum albumin, handgrip strength and kidney disease-specific quality of life. The malnutrition-inflammation score also decreased significantly in the probiotic group, whereas hospitalization, predefined nutritional response, mortality and adverse-event outcomes did not differ significantly between groups.

These findings are best interpreted as evidence of potential biochemical, nutritional, functional and patient-reported benefit rather than proof of an effect on major clinical events. Previous randomized studies of probiotic or

synbiotic treatment in hemodialysis have produced variable inflammatory results. Soleimani et al reported that 12 weeks of multistrain probiotic supplementation in patients with diabetes receiving hemodialysis improved glycemic measures and reduced selected markers of inflammation and oxidative stress.¹⁵ Haghighat et al found that both probiotic and synbiotic regimens modified endotoxin-related and inflammatory measures, although the magnitude of benefit differed between the interventions.¹⁶ Kooshki et al similarly reported improvements in inflammatory, oxidative-stress and lipid variables after synbiotic supplementation.¹⁷ In contrast, Mirzaeian et al observed selective rather than uniform effects on protein-bound uremic toxins and systemic inflammation, emphasizing that changes in gut-derived metabolites do not necessarily translate into parallel changes in every circulating inflammatory biomarker.¹⁸

Longer and more intensive probiotic regimens have also yielded mixed results. In a double-blind trial, Lim et al demonstrated a reduction in indoxyl sulfate but no consistent improvement in most inflammatory or microbial-translocation markers.¹⁹ Araújo et al evaluated the same four-strain combination used in the present study and found reductions in syndecan-1 and glucose, while conventional inflammatory measures were less consistently affected.²⁰ Collectively, these studies suggest that probiotic activity in kidney failure is likely to be strain- and endpoint-specific.

They also show why a multidimensional assessment may be more informative than reliance on a single biomarker. Evidence relating probiotics to nutritional improvement is similarly evolving. A recent randomized trial by Saad et al found that probiotic and synbiotic supplementation improved body mass index and triceps skinfold thickness, whereas the between-group effect on serum albumin was not significant.²¹ Azad et al reported improvement in subjective global assessment after a fortified synbiotic dessert, but most biochemical, oxidative-stress, inflammatory and quality-of-life measures did not differ between groups.²²

Shariaty et al found reduced hemoglobin variability without a clear increase in mean hemoglobin concentration after probiotic supplementation.²³ In another trial Haghighat et al observed improvements in depression and anxiety scores and selected quality-of-life domains after probiotic or synbiotic treatment.²⁴ A recent meta-analysis across chronic kidney disease populations concluded that probiotics and synbiotics may improve some metabolic and inflammatory outcomes, but substantial heterogeneity and generally small trials limit the certainty and clinical generalizability of pooled estimates.²⁵

The inflammatory markers evaluated in this trial have established prognostic relevance, although they remain surrogate measures rather than validated treatment targets. The neutrophil-to-lymphocyte ratio is inexpensive and readily available and higher values have been associated with reduced survival in chronic hemodialysis cohorts.²⁶ C-reactive protein has long been linked to cardiovascular risk and mortality in dialysis patients, reflecting the central role of the acute-phase response in the malnutrition-inflammation-atherosclerosis pathway.²⁷ Red cell distribution width is influenced by inflammation, iron availability, erythropoietic stress, nutritional deficiency and red-cell survival; higher values have been associated with all-cause and cardiovascular mortality in hemodialysis.²⁸

A concurrent improvement across several of these markers may therefore indicate attenuation of inflammatory burden, but it cannot by itself establish that probiotic treatment will reduce cardiovascular events or mortality. Serum albumin and the malnutrition-inflammation score require similarly cautious interpretation. Low serum albumin is a powerful predictor of mortality in

hemodialysis, but its concentration reflects inflammation, hydration, hepatic synthesis, urinary or dialytic losses and illness severity in addition to nutrient intake.²⁹ The malnutrition-inflammation score was developed as an integrated measure of nutritional and inflammatory burden and has been associated with hospitalization and mortality.³⁰ In a large prospective cohort, higher scores were also associated with poorer quality of life and increased long-term mortality.³¹

Accordingly, the increase in serum albumin and the reduction in MIS observed in the probiotic group are biologically coherent and may reflect improvement in the combined nutritional and inflammatory burden. Nevertheless, both measures remain influenced by comorbidity, hydration status, dietary intake and concurrent illness and should therefore be interpreted as supportive rather than definitive evidence of improved nutritional status.

Physical function and health-related quality of life are particularly relevant because laboratory improvement does not necessarily translate into a benefit perceived by patients. Handgrip strength is a practical marker of muscle function and nutritional reserve and lower baseline strength has been associated with a higher risk of death in both women and men receiving hemodialysis.³² The dialysis outcomes and practice patterns study demonstrated that poorer health-related quality-of-life scores predict mortality and hospitalization independently of major demographic, comorbidity and laboratory factors.³³

Additional DOPPS analyses showed clinically important variation in quality of life across patient groups and confirmed its association with subsequent outcomes.³⁴ The observed changes in handgrip strength and KDQOL-36 therefore extend the potential relevance of probiotic supplementation beyond laboratory biomarkers, although open-label outcome assessment may have increased susceptibility to performance and reporting bias.

The absence of statistically significant differences in hospitalization and mortality is not unexpected in a single-center trial of 60 participants followed for 6 months. These outcomes occur relatively infrequently and require substantially larger samples and longer observation to detect plausible treatment effects. Probiotics are generally well tolerated, but rare cases of bloodstream infection or other invasive infection have been reported, particularly in critically ill or severely immunocompromised individuals and in patients with disrupted intestinal barriers or indwelling vascular devices.³⁵

Moreover, systematic evaluation of microbiota-directed randomized trials has shown that adverse-event definitions, ascertainment and reporting are often incomplete.³⁶ Safety conclusions should therefore be based on active surveillance, strain-level identification when infection occurs and transparent reporting rather

than on the absence of common gastrointestinal symptoms alone. Several factors may explain the inconsistency among microbiota-directed trials in kidney disease. Probiotic effects cannot be assumed to be interchangeable across species or strains and viable dose, formulation, storage conditions, treatment adherence, habitual fiber and protein intake, antibiotic exposure, residual kidney function, dialysis modality and baseline microbiome composition may all modify response. The synergy trial demonstrated that synbiotic treatment could alter the intestinal microbiome and reduce selected microbiome-derived uremic toxins in chronic kidney disease, while also illustrating the influence of diet and antibiotic exposure on treatment response.³⁷

Future hemodialysis trials would be strengthened by combining clinical outcomes with direct microbiome sequencing, intestinal-barrier markers, dietary assessment and measurement of free and total indoxyl sulfate and p-cresyl sulfate. Such designs could distinguish true modification of the gut-kidney axis from nonspecific changes in inflammatory markers.

The strengths of the present study include randomized allocation, a 6-month intervention period, use of a defined four-strain formulation and simultaneous evaluation of inflammatory, nutritional, functional, patient-reported, clinical and safety outcomes.

Important limitations include the single-center design, modest feasibility sample, absence of a placebo, open-label treatment and outcome assessment, lack of an a priori power calculation and the large number of secondary comparisons without multiplicity adjustment. Microbiome composition, gut permeability, dietary intake and microbiota-derived uremic toxins were not measured, preventing direct confirmation of the proposed mechanism.

In addition, the current effect estimates for several outcomes were reconstructed from aggregate summary data. The final manuscript should therefore replace these estimates with the prespecified participant-level mixed-effects and quantile-regression outputs before the results are interpreted as definitive trial findings.

CONCLUSION

Six months of multistrain probiotic supplementation produced favorable signals across systemic inflammation, nutritional status, muscle strength and kidney disease-specific quality of life in adults receiving maintenance hemodialysis, without a detectable effect on short-term hospitalization or mortality.

The findings are consistent with a growing but heterogeneous literature suggesting that selected probiotic and synbiotic formulations may modify components of the gut-kidney-inflammatory axis. Confirmation requires adequately powered, placebo-controlled multicentre trials

using prespecified participant-level analyses, rigorous safety surveillance and integrated microbiome, dietary, uremic-toxin and patient-centered outcome assessment.

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