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ARTICLE

Effect of a Multicomponent Intervention on Pre-Frailty Status Changes in Patients Undergoing Maintenance Hemodialysis: A Randomized Controlled Study

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Abstract

Aims/Background Pre-frailty is common in patients undergoing maintenance hemodialysis (MHD). Without proper management, it can quickly worsen and progress into frailty, leading to various adverse clinical outcomes. Therefore, timely interventions for pre-frail MHD patients are crucial. However, the response of pre-frail MHD patients to such interventions is currently unclear. This study evaluated the effect of a multicomponent intervention on changes in pre-frailty status, risk factors for frailty, quality of life, and clinical outcomes in pre-frail patients undergoing MHD.

Methods Sixty MHD patients were randomly assigned to intervention (received a 12-week multicomponent intervention) and control (received standard care) groups, with 30 participants per group, between February and May 2018. Data were collected at baseline and at 3 and 9 months thereafter. Analyzed outcomes included changes in pre-frailty status, frailty risk factors (such as albumin level, pain, and anxiety), quality of life, and clinical outcomes during the follow-up period.

Results Data from a total of 58 MHD patients were collected at three time points. At week 12, frailty scores were 0.9 points lower in the intervention group compared to the control group ($p = 0.007$). The intervention group showed a 26.2% higher proportion of patients who improved from pre-frailty to non-frailty compared to the control group ($p = 0.029$), and a 25.9% lower proportion of patients who progressed from pre-frailty to frailty ($p = 0.021$). Additionally, improvements in albumin levels, pain, anxiety, and quality of life were more significant in the intervention group (all $p < 0.05$). Although there were fewer incidents of falls and rehospitalizations in the intervention group during follow-up, these differences did not reach statistical significance (all $p > 0.05$).

Conclusion This study validates the effectiveness and practicality of a multicomponent intervention in improving pre-frailty status, frailty risk factors, and quality of life in patients undergoing MHD.

Clinical Trial Registration Chinese Clinical Trial Registry (ChiCTR-IOR-17012176).

Key words: pre-frailty; frailty; maintenance hemodialysis; quality of life; intervention; randomized controlled trial

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Introduction

Frailty, defined as a cluster of syndromes marked by reduced physiological reserve or multisystem dysregulation, amplifies an individual's susceptibility to stress, making them vulnerable to clinical adverse events (Fried et al, 2001). The

prevalence of frailty in maintenance hemodialysis (MHD) patients is as high as 35.3% (Ye et al, 2023), attributable to age-related physiological decline, organ function impairment, and pathophysiological changes associated with chronic kidney disease and hemodialysis (Chao and Lin, 2021). Frailty has broad implications, including a strong correlation with quality of life (QOL) (Ye et al, 2018), vascular access thrombosis (Luo et al, 2022), independence levels, mood, cognition, hospitalizations, and mortality in affected individuals (Fu et al, 2021; Jafari et al, 2020; McAdams-DeMarco et al, 2013).

Conversely, pre-frailty characterizes the transitional phase between health and frailty, signifying an early and potentially reversible stage preceding the onset of established frailty (Chang et al, 2021). Surprisingly, pre-frailty shows an even higher prevalence of 43.3% among MHD patients, surpassing the prevalence of frailty itself (Ye et al, 2023). Pre-frail elders exhibit over five times higher frailty prevalence compared to their non-frail counterparts (Ofori-Asenso et al, 2019), and given the connection between pre-frailty and nutrition (Chang and Lin, 2016), effective management strategies for pre-frail patients undergoing MHD are pivotal in stalling and preventing frailty onset in this population.

However, there has been minimal effort to address frailty among MHD patients (Markossian et al, 2022). Current interventions primarily focus on exercise-based approaches, such as cycling exercise during dialysis (Kim et al, 2023; Young et al, 2020), aerobic exercise between dialysis sessions (Yi, 2019), and multicomponent exercises incorporating endurance, strength, and flexibility training (Lorenz et al, 2023). Additional strategies include oral high-energy nutritional supplements (Wu et al, 2020), moxibustion at the navel (Li et al, 2022), and other multicomponent interventions (Arias-Guillén et al, 2023; Bogataj et al, 2022). Despite some studies investigating frailty-related interventions for MHD patients, these efforts tend to be more singular in nature, with fewer employing comprehensive multicomponent approaches.

A systematic review has highlighted the efficacy of combined interventions compared to single-domain approaches in managing frailty (Dedeyne et al, 2017). Given that frailty often results from cumulative declines across various physiological systems, interventions should ideally target multiple domains. Previous studies (Arias-Guillén et al, 2023; Ng et al, 2017) have also shown promise in multicomponent interventions for mitigating frailty. However, these investigations have primarily focused on frail community-dwelling elders, with limited research on pre-frail populations among individuals with MHD, yielding controversial results.

For instance, one study found that a combination of exercise and nutritional interventions did not reverse pre-frailty in community-dwelling elders (Tay et al, 2022). In contrast, another study demonstrated that a multicomponent intervention combining exercise, nutrition, and polypharmacy management improved frailty status, physical performance, and strength among pre-frail elders (Tan et al, 2022). Moreover, a prospective observational study involving hemodialysis patients indicated that a multicomponent intervention encompassing nutritional, physical, cognitive, and emotional components effectively altered the pre-frail status of these patients, contradicting previous findings (Arias-Guillén et al, 2023).

Therefore, further investigation into the effectiveness of multicomponent interventions on pre-frailty among MHD patients is warranted. Additionally, while numerous studies have explored nutrition and exercise in hemodialysis patients, previous exercise interventions targeting frailty in MHD patients have predominantly focused on lower extremity exercises, overlooking grip strength training in the upper extremities—a crucial frailty phenotype. Moreover, pain is a significant risk factor for frailty in MHD patients (Ye et al, 2023), yet the efficacy of pain management as an intervention for frail or pre-frail MHD patients remains unexplored.

To address these gaps, we developed a comprehensive multicomponent intervention program that integrates frailty phenotypes with influential factors specific to MHD patients. This study aimed to evaluate the impact of this intervention on changes in pre-frailty status, as well as on risk factors such as albumin levels, pain, anxiety, QOL, and clinical outcomes during follow-up among pre-frail patients undergoing MHD.

Methods

Study Design

This study was conducted at the blood purification center of the First People's Hospital of Lianyungang, Jiangsu Province, a Grade III Level-A public hospital and the largest facility of its kind in Lianyungang City. It was designed as a randomized controlled trial, and the study flowchart is depicted in Fig. 1. Pre-frail participants were randomly assigned to either the intervention or control group, with 30 participants in each group. Those in the intervention group underwent a 12-week multicomponent intervention, while participants in the control group received standard care.

Participant

In this study, we recruited 60 pre-frail participants undergoing MHD at the blood purification center between February and May 2018. Inclusion criteria were as follows: (1) aged between 18 and 80 years; (2) receiving hemodialysis for at least three months with stable medical status; (3) meeting one or two indicators of the Fried frailty phenotype (Fried et al, 2001); (4) possessing clear consciousness without communication barriers; (5) having no physical disability and able to ambulate independently; (6) willing to participate in the multicomponent intervention and provide informed consent. Exclusion criteria were applied to participants who: (1) had hypertension (systolic pressure $\geq$180 mmHg or diastolic pressure $\geq$110 mmHg) or pulmonary hypertension; (2) had severe thrombophlebitis, renal osteodystrophy, acute lower extremity thrombosis, or spinal, joint, or muscle diseases that hindered exercise; (3) had active malignancies; (4) were experiencing acute infections, acute heart failure, or acute/critical illnesses such as severe sequelae of cerebrovascular diseases; (5) had a history of mental illness, amputation, or had undergone or were awaiting transplantation.

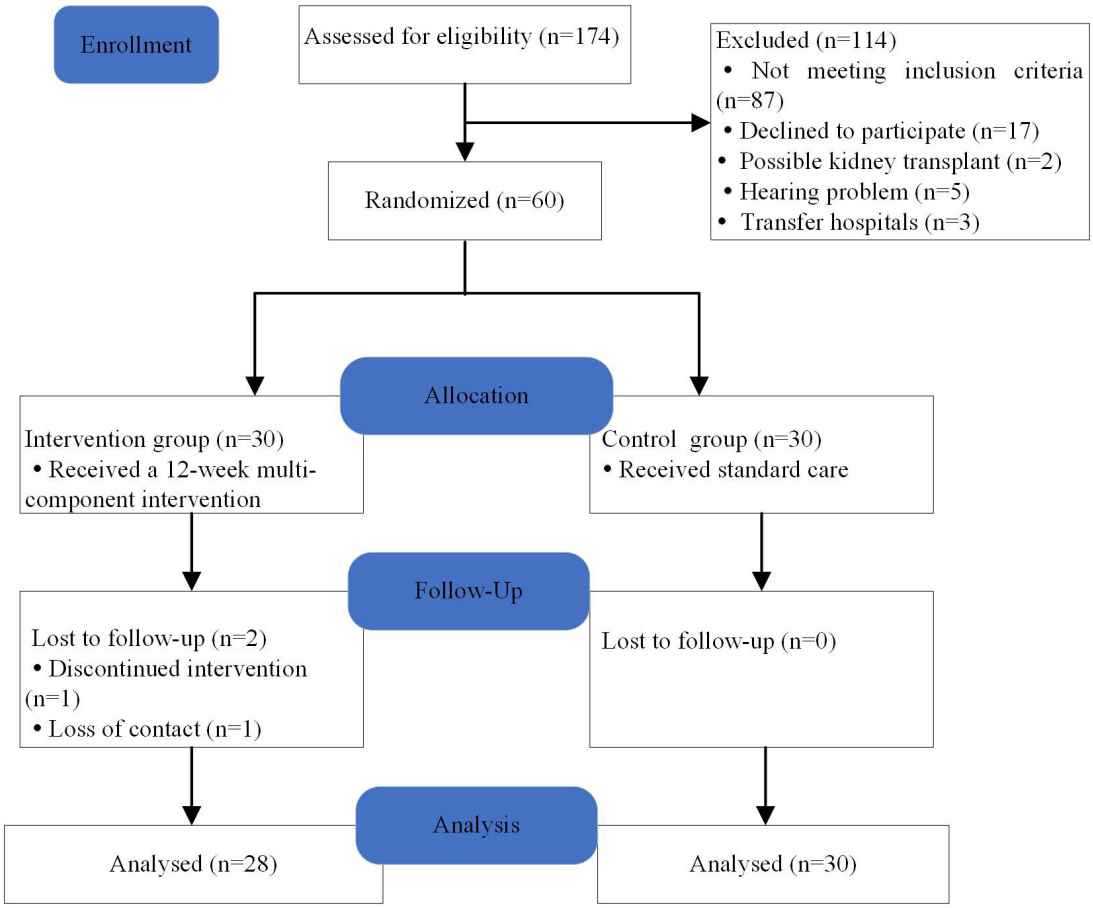

Fig. 1. The consolidated standards of reporting trial diagram.

Sample Size

This study utilized a parallel randomized controlled trial design, where participants were assigned to either the intervention (multicomponent intervention) or control (standard care) group. The primary outcome measure assessed was the frailty score. According to findings from a previous study (Ng et al, 2015), the multicomponent intervention group showed an average frailty score of 1.3 ± 0.84, whereas the control group had a score of 2.1 ± 0.81.

Using PASS (version 11.0, NCSS, LLC, Kaysville, UT, USA) with $\alpha = 0.05$ (two-tailed) and $\beta = 0.10$, a sample size calculation determined that 23 participants per group were necessary. Accounting for a 10% dropout rate, the study aimed to recruit 26 participants in each group. Therefore, a total of 60 participants were enrolled based on practical clinical considerations.

Randomization

Upon expressing willingness to participate, individuals were required to formally sign an informed consent form. To randomly allocate pre-frail participants into their respective groups, a systematic approach was employed: Initially, 60 random numbers were generated using Excel (version 14.0.7015.1000, Microsoft

Corporation, Washington, DC, USA). The first 30 numbers were assigned to the intervention group, while the subsequent 30 were assigned to the control group.

To mitigate the risk of potential cross-contamination between groups, participants assigned to the intervention and control groups were housed on different floors within the blood purification center. Due to the nature of the interventions requiring active participation from both participants and investigators, blinding of group assignments was not feasible.

Intervention Group

Participants allocated to the intervention group underwent the multicomponent intervention for a duration of 12 weeks.

Multicomponent Intervention Program

The intervention program was developed by synthesizing insights from previous research, integrating the Fried frailty phenotypes (Fried et al, 2001), and incorporating inputs from a medical staff workshop. Initially, an extensive literature review was conducted to gather information from studies focusing on frailty factors in patients undergoing MHD. This was followed by a cross-sectional survey involving MHD patients across six Grade II Level-A or higher public hospitals' blood purification units, which identified several contributing factors to frailty. These factors included advanced age, female gender, obesity, low household income, lack of exercise, primary diagnosis of diabetes, shorter duration of dialysis ($\leq$12 months), and comorbidities such as congestive heart failure and other cardiac diseases, as well as pain, albumin levels (Ye et al, 2023), and anxiety. Among these factors, exercise, albumin levels, pain, and anxiety were identified as intervenable factors strongly associated with frailty risk, while others were addressed in the management of additional frailty risk factors. Based on these findings, a comprehensive multicomponent intervention program was devised, consisting of five key components: nutritional interventions, intradialytic resistance exercise, grip training, pain management, and monitoring and management of other frailty risk factors. Additionally, a collaborative seminar was convened with specialized professionals including blood purification specialist nurses, nephrologists, nutritionists, exercise rehabilitation physicians, psychological counselors, and pain specialist nurses. This session was dedicated to formulating a tailored intervention plan specifically designed for pre-frail patients.

Prior to implementation, each intervention protocol underwent rigorous review, and study staff received comprehensive training to ensure proficiency and feasibility in administering the intervention program. The interventions themselves were personalized for each participant, based on initial assessments of frailty phenotypic characteristics and the identified risk factors from the earlier cross-sectional survey. Detailed specifics of the intervention program are outlined below.

Nutrition Interventions

The protocol encompassed the following steps:

(1) Assessment: The nutritional status of patients was evaluated using either the Nutritional Screening Scale or the Body Composition Analyzer.

(2) Dietary Survey: A three-day dietary survey was conducted, which included one dialysis day, one non-dialysis day, and one weekend day, using the 24-hour dietary recall method. Subsequently, collected dietary data underwent analysis using nutrient analysis software.

(3) Dietary Guidance: Based on assessment outcomes, results from the dietary survey, recommended nutrient intake for daily diets of MHD participants, participants' physical activity, and relevant biochemical indicators, personalized dietary guidance was provided. This guidance was complemented by a series of three nutritional knowledge lectures, each lasting 40–60 minutes, facilitating direct communication between participants (or their families) and the research team.

(4) High-Protein Diet Provision: Given the heightened nutritional losses and catabolism in hemodialysis patients, they experience an increased resting energy expenditure of 8%–16% compared to normal subjects (Lindholm et al, 1998). The literature suggests dialysis patients may require an additional 0.2 to 0.4 g/kg/day of protein supplementation, with dialysis meals accounting for at least 1/7 of daily meals (Kalantar-Zadeh and Ikizler, 2013). In this study, participants received a high-protein diet three times a week during hemodialysis sessions, administered by the hospital's nutritional cafeteria and supervised by the charge nurse. This provision included 2 hard-boiled egg whites (providing 11.6 g of protein and 60 kcal) and 1 pork bun (providing 8.0 g of protein and 241 kcal), totaling 19.6 g of protein and 301 kcal. The high-protein diet aimed to increase protein intake by approximately 30% and energy intake by around 20%.

Intradialytic Resistance Exercise

Given the benefits of resistance exercise for weaker patients and the positive impact of incorporating exercise into the dialysis routine for patient participation and tolerance (Johansen, 2005), this study implemented supervised progressive resistance exercises during dialysis sessions. Participants engaged in this exercise regimen three times per week, typically during the first 1–2 hours of dialysis, preceded by a 5-minute warm-up.

The exercise routine involved alternately raising and lowering both legs, performing 10 repetitions per leg for a total of 10 sets. Initially, weight-bearing in the lower extremities began without any additional load during the first week. Subsequently, the resistance gradually increased by 0.5 kg per week using sandbags until participants could comfortably manage 5 kg of weight-bearing in both lower extremities.

Throughout the exercise sessions, participants' vital signs were closely monitored using a cardiac monitor to observe any physiological changes. They were encouraged to exercise at an intensity that induced slight fatigue and perspiration, while ensuring they did not experience palpitations or shortness of breath. Participants were instructed to immediately cease exercise if they encountered chest pain, palpitations, or any form of discomfort.

Grip Training

Low hand grip strength is closely linked to reduced functional capacity, increased inflammation, and heightened mortality risk in individuals undergoing MHD (Lopes et al, 2022; Vogt et al, 2016). Given that low grip strength is also considered one of the frailty phenotypes (Fried et al, 2001), enhancing grip strength is crucial for these patients.

In this intervention, participants began with a 5-minute warm-up following 15 minutes of hemodialysis. They then engaged in grip strength training using an elastic ball held in their non-dialyzed hand. Participants gradually applied pressure to the ball until reaching maximum grip, holding this tension for 3 to 5 seconds before releasing. Each set consisted of 10 repetitions, with participants completing a total of 10 sets per session.

Throughout the exercise, individuals were encouraged to maintain and progressively increase resistance using personalized adjustment methods based on individual sensation and recorded tables tracking movements, fatigue, and sensory feedback. Participants underwent grip strength training three times a week, with each session lasting between 30 to 45 minutes.

Pain Management

Participants' pain levels in the intervention group were monitored during each dialysis session using a visual analogue scale (VAS). Those reporting scores between 1 and 3 were assessed daily, while those scoring between 4 and 6 were evaluated every 8 hours. Participants with scores exceeding 6 were closely monitored. Participants recording a VAS score above 3, experiencing changes in pain characteristics or locations, or developing new associated symptoms were promptly referred to physicians for appropriate treatment. Guidance was provided on managing pain relief medications, making dietary adjustments, optimizing rest environments, and receiving psychological support. Pain associated with dialysis procedures, such as arteriovenous fistula puncture, dialysis-induced headaches, or muscle spasms, was addressed using various techniques including topical lidocaine cream, improved puncture techniques, aromatherapy, and playing classical music. Participants experiencing severe depression or anxiety were referred to a psychological counseling clinic for further treatment.

Monitoring and Management of Other Frailty Risk Factors

Participants underwent monthly evaluations to assess additional potential risk factors contributing to frailty, including lifestyle factors such as smoking, alcohol consumption, sleep quality, and engagement in leisure activities. Researchers systematically reviewed hemodialysis records to compile comprehensive data, including dry weight, ultrafiltration volume, vascular access details, vital signs, specifics of the dialysis regimen, symptoms related to dialysis, existing comorbidities, medication usage, and biochemical parameters. These findings were communicated to participants or their caregivers either verbally or in written form. Patients were educated about the importance of effectively managing these identified risk factors to prevent the onset or progression of frailty. Motivational support was provided to

encourage active engagement in addressing and managing these risk factors effectively.

Control Group

Participants in the control group received standard care administered by a healthcare team consisting of a nurse and a supervising physician. They attended health lectures alongside participants in the trial group and received identical food provisions, but without direct supervision. During dialysis sessions, nurses from the blood purification center engaged with control group participants in face-to-face interactions three times, each session lasting approximately 30 minutes. These interactions aimed to provide oral information on essential knowledge and routine care for renal diseases, following guidelines outlined in the Internal Medicine Nursing textbook.

Outcome Measurements

Primary Outcome

The primary outcome of the study was the change in participants' pre-frailty status, categorized into improvements, deteriorations, and overall frailty scores. Improvement referred to participants transitioning from a pre-frail state to non-frailty, while deterioration indicated progression from pre-frailty to frailty. The participants' frailty score was assessed using Fried's definition of frailty phenotypes (Fried et al, 2001), which includes five indicators: (1) Weight loss: Defined as an unexpected dry weight loss exceeding 5% in the past year. (2) Slow gait speed: Assessed by the time taken to walk fifteen feet, adjusted for height and sex. (3) Low grip strength: Measured three times using a handheld dynamometer (EH101, Senssun Weighing Apparatus Group Ltd., Guangdong, China), with the maximum value adjusted for sex and body mass index (BMI). (4) Low physical activity: Evaluated using the China International Physical Activity Questionnaire (Macfarlane et al, 2007), identifying low physical activity by weekly calorie expenditure thresholds ($<$383 kcal for men and $<$270 kcal for women). (5) Fatigue: Assessed using specific entries from the Center for Epidemiologic Studies Depression Scale (Orme et al, 1986), scoring based on the frequency of feeling overwhelmed or inability to walk forward in the past week. Participants meeting any one of these frailty indicators received a score of 1, with a total score ranging from 0 to 5. A score of 0 indicates non-frailty, 1–2 indicates pre-frailty, and $\geq$3 indicates frailty. This validated frailty assessment method has shown predictive validity for mortality and hospitalization rates among hemodialysis patients in cohort studies (McAdams-DeMarco et al, 2013).

Secondary Outcomes

The secondary outcomes of the study included participants' frailty risk factors (albumin levels, pain, anxiety), QOL, and clinical outcomes during follow-up. Here's how each outcome was assessed:

(1) Albumin levels: Venous blood samples were collected from all participants before their hemodialysis sessions to measure albumin levels.

(2) Pain: Pain levels were assessed using a visual analogue scale (VAS), ranging from 0 mm (indicating no pain) to 100 mm (indicating extreme pain). Higher scores on the VAS corresponded to more severe pain. A score greater than 3 indicated moderate to severe pain. The VAS is known for its sensitivity to small differences in pain intensity and has high repeatability compared to verbal description scales (Rosier et al, 2002).

(3) Anxiety: Anxiety status was evaluated using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) developed by Zigmond and Snaith (1983). This subscale comprises seven items, each scored on a four-point scale from 0 to 3. The total anxiety score is obtained by summing the scores of all items, with higher scores indicating more severe anxiety. Anxiety subscale scores are categorized as follows: 0–7 (negative), 8–10 (mild), 11–14 (moderate), and 15–21 (severe).

The participants' QOL was assessed using the 36-item Short Form Health Survey Questionnaire (SF-36), adapted for the Chinese population by Li et al (2002). This questionnaire comprises 36 items organized into 8 dimensions: physical functioning, physical role limitations, bodily pain, general health perceptions, vitality, social functioning, emotional role limitations, and mental health. The first four dimensions contribute to the Physical Component Summary (PCS), while the latter four contribute to the Mental Component Summary (MCS). Each dimension is scored on a scale from 0 to 100 points, where higher scores indicate better health status (Wang et al, 2020).

Clinical outcomes were evaluated for frailty-related adverse events, including falls, rehospitalization, and mortality, observed in participants at the conclusion of the 12-week intervention and during the 6-month follow-up period. These outcomes provided insight into the impact of the multicomponent intervention on reducing frailty-related complications and improving overall clinical outcomes among the study participants.

Data Collection

Data were collected at three specific time points throughout the study: at recruitment (T1), participants provided basic information and underwent assessments for frailty, albumin levels, anxiety, and QOL. At the end of the 12-week intervention period (T2), assessments were conducted again for frailty, albumin levels, anxiety, and QOL to evaluate the impact of the multicomponent intervention. During the 6-month follow-up (T3), information regarding falls, rehospitalizations, and participant deaths was obtained either by medical staff or through telephone inquiries. These time points were critical for monitoring changes in frailty status, health indicators, and clinical outcomes over the course of the study, providing comprehensive data on the effectiveness and sustained impact of the intervention.

Data Analyses

Statistical analyses were conducted using SPSS (version 21.0, IBM-SPSS Statistics, Chicago, IL, USA). The normality and homogeneity of variance of baseline continuous variables were assessed using the Shapiro-Wilk test and Levene's test,

respectively. Normally distributed variables were presented as mean ± standard deviation ($\bar{x} \pm s$), and intergroup comparisons were performed using the *t*-test (for equal variances) or the corrected *t*-test (for unequal variances). Non-normally distributed variables were reported as median with interquartile range (IQR), and intergroup comparisons were made using the Mann-Whitney U test.

Categorical data were expressed as counts and percentages [n (%)], and intergroup comparisons were conducted using the χ^2 test or the continuity-corrected χ^2 test. Analysis of covariance was utilized to assess the impact of the intervention on the 12-week outcomes and clinical events, adjusting for baseline values. Least-square (LS) means were calculated to estimate intervention effects, and residual errors' normality was assessed using the Shapiro-Wilk test.

For count data, the χ^2 test was employed. Effect sizes for the 12-week outcomes and clinical events were reported as differences in LS means or rates between the intervention and control groups. The significance level was set at 0.05 for two-tailed tests.

Results

The initial screening process involved 174 patients between February and May 2018 to assess eligibility for the study. Eventually, 60 pre-frail participants who met the criteria were enrolled, with an equal distribution into the intervention and control groups at a 1:1 ratio. During the intervention period, no serious adverse events such as slipping of vascular access or falling out of bed occurred in the intervention group. One participant withdrew due to disinterest, and another was lost to follow-up after transferring to another hospital. There were no dropouts in the control group. As depicted in Fig. 1, the final analysis included data from 58 participants who completed all assessments.

Description of the Participants' Demographic and Disease Characteristics

The participants had a mean age of 50.40 ± 12.46 years, with a median dialysis vintage of 53.00 (interquartile range: 21.75–75.75) months. Among these individuals, 62.1% were male, and 94.8% were married. Additionally, 5.2% of the participants lived alone, while 55.2% reported having low household income, and only 1.7% were employed. In terms of primary diagnoses, 19 participants (32.8%) had glomerulonephritis, 16 (27.6%) had hypertensive nephritis, 6 (10.3%) had diabetic nephropathy, and 17 (29.3%) had obstructive nephropathy or other types of primary nephritis. Importantly, at baseline, there were no statistically significant differences observed between the intervention and control groups regarding demographic characteristics or outcome variables ($p < 0.05$) (Table 1).

Table 1. Comparison of patients' demographic and clinical characteristics, by group (n = 58).

Variables		Overall (n = 58)	Intervention (n = 28)	Control (n = 30)	$t/\chi^2/z$	p-value
Age (years), mean ± SD		50.40 ± 12.46	51.57 ± 13.62	49.3 ± 11.39	0.691	0.493
Sex, n (%)	Male	36 (62.1)	18 (64.3)	18 (60.0)	0.113	0.737
	Female	22 (37.9)	10 (35.7)	12 (40.0)		
Marital status, n (%)	Married	55 (94.8)	27 (96.4)	28 (93.3)	<0.001	1.000
	Unmarried	3 (5.2)	1 (3.6)	2 (6.7)		
BMI (kg/m^2), mean ± SD		22.81 ± 3.26	22.33 ± 3.00	23.26 ± 3.47	–1.083	0.283
Living alone, n (%)	Yes	3 (5.2)	3 (10.7)	0 (0.0)	1.557	0.212
	No	55 (94.8)	25 (89.3)	30 (100.0)		
Residential area, n (%)	Urban	26 (44.8)	13 (46.4)	13 (43.3)	0.056	0.813
	Rural	32 (55.2)	15 (53.6)	17 (56.7)		
Educational level, n (%)	Primary school or below	21 (36.2)	9 (32.1)	12 (40.0)	0.437	0.804
	Junior high school	24 (41.4)	12 (42.9)	12 (40.0)		
	Senior high school or above	13 (22.4)	7 (25.0)	6 (20.0)		
Employment, n (%)	Yes	1 (1.7)	1 (3.6)	0 (0.0)	0.001	0.972
	No	57 (98.3)	27 (96.4)	30 (100.0)		
Per capita monthly household income, n (%)	≥300 dollars	26 (44.8)	13 (46.4)	13 (43.3)	0.056	0.813
	<300 dollars	32 (55.2)	15 (53.6)	17 (56.7)		
Medical expense payment method, n (%)	Public fee/urban medical insurance	27 (46.6)	14 (50.0)	13 (43.3)	0.259	0.611
	New rural cooperative medical system/self-pay	31 (53.4)	14 (50.0)	17 (56.7)		
Smoking status, n (%)	Yes	7 (12.1)	4 (14.3)	3 (10.0)	0.009	0.922
	No	51 (87.9)	24 (85.7)	27 (90.0)		
Primary diagnosis, n (%)	Glomerulonephritis	19 (32.8)	13 (46.4)	6 (20.0)	5.296	0.151
	Hypertension	16 (27.6)	5 (17.9)	11 (36.7)		
	Diabetes	6 (10.3)	3 (10.7)	3 (10.0)		
	Obstructive or other	17 (29.3)	7 (25.0)	10 (33.3)		
Multimorbidity, n (%)	<3 types	46 (79.3)	22 (78.6)	24 (80.0)	0.018	0.893
	≥3 types	12 (20.7)	6 (21.4)	6 (20.0)		

Table 1. Continued.

Variables		Overall (n = 58)	Intervention (n = 28)	Control (n = 30)	$t/\chi^2/z$	*p*-value
Polypharmacy, n (%)	<3 types	17 (29.3)	11 (39.3)	6 (20.0)	2.600	0.107
	≥3 types	41 (70.7)	17 (60.7)	24 (80.0)		
Frequency of dialysis, n (%)	3 to 4 times a week	44 (75.9)	19 (67.9)	25 (83.3)	1.894	0.169
	2 times per week	14 (24.1)	9 (32.1)	5 (16.7)		
Vascular access, n (%)	Arteriovenous fistula	56 (96.6)	27 (96.4)	29 (96.7)	0.000	1.000
	Central venous catheterization	2 (3.4)	1 (3.6)	1 (3.33)		
Dialysis age (month), median (IQR)		53.00 (21.75–75.75)	48.50 (16.00–76.25)	558.00 (24.00–75.75)	–0.514	0.607
Hemoglobin level (g/L), mean ± SD		100.76 ± 18.09	103.68 ± 15.84	98.03 ± 19.85	1.192	0.238
Albumin level (g/L), mean ± SD		39.5 ± 3.27	39.40 ± 3.15	39.58 ± 3.42	0.208	0.836
Anxiety, median (IQR)		7.50 (3.00–11.00)	7.00 (3.00–9.00)	8.50 (3.00–12.00)	–0.641	0.521
Frailty score, mean ± SD		1.53 ± 0.54	1.61 ± 0.57	1.47 ± 0.51	0.996	0.324
Grip strength (kg), mean ± SD		28.32 ± 8.90	28.19 ± 9.76	28.44 ± 8.18	–0.108	0.915
Paces (s), mean ± SD		5.28 ± 1.15	5.34 ± 1.33	5.22 ± 0.96	0.393	0.696
Weight loss, n (%)	Yes	14 (24.1)	7 (25.0)	7 (23.3)	0.022	0.882
	No	44 (75.9)	21 (75.0)	23 (76.7)		
Low physical activity, n (%)	Yes	27 (46.6)	14 (50.0)	13 (43.3)	0.259	0.611
	No	31 (53.4)	14 (50.0)	17 (56.7)		
Fatigue, n (%)	Yes	22 (37.9)	10 (35.7)	12 (40.0)	0.113	0.737
	No	36 (62.1)	18 (64.3)	18 (60.0)		
Pain score median (IQR)		7.50 (0–28.00)	0 (0–27.50)	15.55 (0–30.50)	–0.150	0.881
Pain level, n (%)	≤3	45 (77.6)	22 (78.6)	23 (76.7)	0.030	0.862
	>3	13 (22.4)	6 (21.4)	7 (23.3)		
PCS, mean ± SD		52.05 ± 13.45	52.61 ± 13.99	51.53 ± 13.14	0.301	0.764
MCS, mean ± SD		52.61 ± 19.99	53.66 ± 19.51	51.63 ± 20.72	0.383	0.703

Abbreviations: BMI, body mass index; PCS, Physical Component Summary; MCS, Mental Component Summary; IQR, interquartile range.

Table 2. Comparisons of pre-frailty status changes, risk factors for frailty, quality of life in maintenance hemodialysis (MHD) patients between the intervention and control groups (n = 58).

Variables		Intervention group (n = 28)	Control group (n = 30)	Effect size (95% CI)	χ^2/F	*p*-value
Become better	Non-frailty	12 (42.9)	5 (16.7)	26.2 (2.68, 46.53)	4.795	0.029
	Pre-frailty and frailty	16 (57.1)	25 (83.3)			
Become worse	Non-frailty and pre-frailty	25 (89.3)	19 (63.3)	25.9 (3.81, 45.10)	5.327	0.021
	Frailty	3 (10.7)	11 (36.7)			
Frailty score		1.13 ± 0.24	2.05 ± 0.23	–0.9 (–1.58, –0.26)	7.771	0.007
Grip strength (kg)		29.87 ± 0.61	26.82 ± 0.59	3.05 (1.34, 4.76)	12.816	0.001
Paces (s)		4.87 ± 0.18	5.55 ± 0.17	–0.68 (–1.17, –0.19)	7.662	0.008
Weight loss	Yes	3 (10.7)	8 (26.7)	15.95 (–4.72, 35.06)	2.398	0.121
	No	25 (89.3)	22 (73.3)			
Low physical activity	Yes	5 (17.9)	15 (50.0)	32.14 (7.68, 51.72)	6.623	0.010
	No	23 (82.1)	15 (50.0)			
Fatigue	Yes	6 (21.4)	11 (36.7)	15.24 (–8.15, 36.29)	1.623	0.203
	No	22 (78.6)	19 (63.3)			
Albumin level (g/L)		41.55 ± 0.77	39.37 ± 0.75	2.18 (0.03, 4.33)	4.123	0.047
Pain score		10.61 ± 1.96	21.06 ± 1.89	–10.45 (–15.89, –0.49)	14.772	<0.001
Pain level	≤3	27 (96.4)	21 (70.0)	26.4 (6.99, 44.54)	7.089	0.008
	>3	1 (3.6)	9 (30.0)			
Anxiety		4.44 ± 0.75	6.85 ± 0.73	–2.41 (–4.50, –0.32)	5.319	0.025
PCS		68.55 ± 3.29	57.26 ± 3.18	11.29 (2.13, 20.46)	6.099	0.017
MCS		67.59 ± 3.77	56.51 ± 3.64	11.08 (0.57, 21.59)	4.461	0.039

Note: Follow-up data are presented as least-square means with SEs adjusted for baseline value. The effect size represents the difference in least-square means or rates between the intervention and control groups. PCS, Physical Component Summary; MCS, Mental Component Summary.

Table 3. Comparisons of clinical outcomes in MHD patients between the intervention and control groups (n = 58).

Clinical outcomes		Intervention group (n = 28)	Control group (n = 30)	Effect size (95% CI)	χ^2	*p*-value
Fall	Yes	4 (14.3)	7 (23.3)	9.05 (–11.67, 28.63)	0.771	0.380
	No	24 (85.7)	23 (76.7)			
Rehospitalization	Yes	10 (35.7)	12 (40.0)	4.29 (–19.76, 27.48)	0.113	0.737
	No	18 (64.3)	18 (60.0)			
Death	Yes	0	0	NA	NA	NA
	No	28	28			

Note: The effect size represents the difference in least-square means or rates between the intervention and control groups. All *p*-values > 0.05.

Effects of the Intervention on Pre-Frailty Status Changes, Risk Factors for Frailty, QOL, and Clinical Outcomes in Pre-Frail Participants Undergoing MHD

The intervention group demonstrated promising outcomes compared to the control group. There was a notable increase of 26.2% in the proportion of participants transitioning from pre-frailty to non-frailty, along with a substantial 25.9% decrease in the proportion progressing from pre-frailty to frailty, compared to the control group. Moreover, the intervention group exhibited a 0.9-point lower frailty score than the control group. The intervention's impact on frailty phenotypes was evident through significant improvements in grip strength, gait speed, and physical activity compared to the control group.

Further analysis using covariance revealed significantly greater improvements in albumin levels, pain, anxiety, and QOL among participants in the intervention group compared to the control group. This suggests that the multicomponent intervention is effective in enhancing pre-frailty status, improving albumin levels, alleviating pain and anxiety, and enhancing QOL among participants (Table 2).

At the 6-month follow-up, although not statistically significant, the intervention group showed a lower incidence rate of falls and hospitalizations compared to the control group. Importantly, no deaths were reported in either group (Table 3). These findings suggest that the multicomponent intervention may positively contribute to reducing the risk of adverse events such as falls and hospitalizations, potentially enhancing overall well-being among participants.

Discussion

This study aimed to investigate the impact of a multicomponent intervention on pre-frailty status changes in patients undergoing MHD. Our findings demonstrate that the intervention effectively improved pre-frail status, addressed frailty-related risk factors such as albumin levels, pain, and anxiety, and enhanced patients' quality of life. During the follow-up period, although not reaching statistical significance, there was a trend suggesting a lower incidence of falls and hospitalizations in the intervention group compared to the control group.

The Multicomponent Intervention Improves Pre-Frailty Status in MHD Participants

Our results demonstrate that the multicomponent intervention effectively improves pre-frailty status in participants with MHD, preventing the progression from pre-frailty to frailty and even reversing some participants to a non-frail state. This aligns with previous findings suggesting that comprehensive interventions can prevent frailty among pre-frail elders by focusing on physical activity, nutrition, poly pharmacy review, and social assessment (Gené Huguet et al, 2018).

In contrast, another study reported that a combined exercise and nutrition intervention did not reverse the pre-frailty state in community-dwelling elders (Tay et al, 2022), which differs from our findings. This discrepancy may be attributed to differences in intervention strategies and participant characteristics. In our study, the intervention program was tailored specifically based on the frailty phenotype of MHD participants and targeted influencing factors of frailty. It included nutrition interventions, intradialytic resistance exercise, grip training, pain management, and monitoring and managing other frailty risk factors, which synergistically interacted to enhance the effectiveness of the intervention.

Given that the energy and protein intake of hemodialysis patients on dialysis days tends to be lower than on non-dialysis days (Afsar et al, 2012), we incorporated high-protein foods during dialysis into our dietary modifications for patients. Previous study has shown that nutritional interventions can enhance the nutritional status and mitigate frailty in participants (Wu et al, 2020), which supports the findings of our study.

Moreover, exercise during dialysis has been shown to reduce inflammatory markers, enhance dialysis adequacy, improve physical activity levels (Dong et al, 2019), and increase grip strength and gait speed while decreasing patient fatigue and frailty (Kim et al, 2023). Importantly, there have been limited intervention studies focusing on grip strength training for frailty in MHD patients, and our study showed significant improvements in patients' grip strength—a critical frailty phenotype—through grip ball training.

Additionally, managing frailty risk factors can play a crucial role in preventing serious complications such as heart failure, disequilibrium syndrome, and infections in patients undergoing MHD, thereby enhancing the overall effectiveness of the intervention.

The Multicomponent Intervention Improves Risk Factors for Frailty (Albumin Levels, Pain, and Anxiety) and QOL in MHD Participants

Patients undergoing MHD often require protein-rich supplementation during dialysis to counteract the loss of circulating amino acids and accelerated muscle protein metabolism (Macfarlane et al, 2007). Consistent with prior research, our study corroborates findings that high-protein food intake during dialysis can help increase albumin levels (Rhee et al, 2017). However, we did not observe significant differences in weight loss between the intervention and control groups, which might be attributed to the relatively short intervention period. Future studies should consider extending the intervention duration to verify our results comprehensively.

In this study, pain management was introduced for the first time in a frailty intervention for MHD patients. Our findings indicated that 22.4% of patients experienced moderate or higher levels of pain. The multicomponent intervention significantly reduced pain scores, albeit modestly by 1 point. Notably, only one participant in the intervention group reported moderate or higher pain levels, compared to nine in the control group with scores >3, indicating a statistically significant difference. Given that pain is a significant risk factor for frailty and is prevalent among MHD patients, interventions targeting frailty in this population should prioritize effective pain management strategies.

Furthermore, our investigation revealed that the multicomponent intervention significantly alleviated anxiety among pre-frail participants. Tailored to frailty phenotypes and relevant influencing factors, this intervention included components that fostered peer support within group settings. Peer support plays a crucial role in comforting and assisting individuals, providing them with a platform to share experiences, concerns, and thoughts without fear of judgment (Yang et al, 2022). Such supportive environments often contribute to reducing anxiety symptoms by enabling patients to find solace in shared experiences with their peers.

In this study, we observed a significant improvement in the QOL among pre-frail participants in the intervention group. This improvement can be attributed to the positive impact of the multicomponent intervention on various frailty phenotypes, such as increased grip strength, improved gait speed, and enhanced physical activity. These factors are known to influence the QOL of patients undergoing MHD (Ye et al, 2018). Our study employed a multidisciplinary team comprising experienced hemodialysis nurses and various professionals who provided comprehensive care tailored to frailty management in MHD participants. This interdisciplinary approach facilitated effective collaboration between different specialities, allowing us to address complex issues comprehensively. Participants benefited from timely access to specialized care and comprehensive assistance from nurses when facing challenges, which likely helped prevent or reduce complications, alleviate physical discomfort, mitigate anxiety, and ultimately contributed to an overall enhancement in QOL. Thus, the integrated approach of our multicomponent intervention, coupled with interdisciplinary teamwork and specialized care, played a pivotal role in improving the QOL of pre-frail participants undergoing MHD in our study.

The Multicomponent Intervention Had an Impact on the Clinical Events of Participants

Throughout the follow-up period, the intervention group experienced lower rates of falls and rehospitalization compared to the control group, although these differences did not reach statistical significance. Notably, there were no fatalities recorded in either group. This observation may be attributed to the study's relatively short duration and the participants' pre-frailty status, which typically involves mild conditions, leading to a lower incidence of frailty-related clinical events. As a recommendation, future research could focus on including frail patients to enable a more comprehensive comparison of clinical outcomes between pre-frail and frail individuals following multicomponent interventions.

Strengthens

Our study has several notable strengths. Firstly, we utilized the Fried frailty phenotypes for assessing frailty, enabling meaningful comparisons with diverse populations and enhancing the generalizability of our findings. Secondly, by focusing on pre-frail patients undergoing MHD, we differentiated our study from those involving frail patients, thereby addressing a group with relatively better overall health. The integration of the intervention within dialysis sessions facilitated its execution by healthcare practitioners and improved patient compliance. Thirdly, our intervention strategy was innovative in that it was tailored based on frailty phenotypes and relevant influencing factors. This targeted approach aimed to address critical frailty domains specific to MHD patients, making our intervention more comprehensive and effective.

Limitations

Our study has several limitations that should be noted. It was a single-center trial conducted with a relatively small sample size and over a limited timeframe. Therefore, the results may not fully capture the complexity and diversity of interventions for frailty in MHD patients.

To strengthen the robustness and applicability of our findings, future research should focus on conducting multi-center studies with larger sample sizes and extended follow-up periods. This approach will enable a more comprehensive validation and refinement of intervention protocols tailored for frailty management in MHD patients.

Conclusion

This study developed and implemented a multicomponent intervention program based on frailty phenotypes and their influencing factors in pre-frail MHD patients. The results demonstrated the effectiveness and safety of this intervention in improving prefrailty status, albumin levels, pain, anxiety, and QOL among this patient population. The intervention program included nutritional interventions and intradialytic resistance exercise, along with often-overlooked components such as grip training, pain management, and monitoring of frailty risk factors. This comprehensive approach made the program informative and easy for healthcare professionals and patients to learn and implement. Materials used in the intervention, such as high-protein diets, sandbags, and elastic balls, were readily available and affordable. Importantly, the intervention was primarily conducted during dialysis sessions, allowing healthcare workers to observe and supervise patients easily, particularly during resistance exercise and grip training. No adverse events related to the intervention occurred, ensuring patient safety and maximizing its effectiveness.

Key Points

- The pre-frailty state of MHD patients can be effectively reversed through intervention.
- The multicomponent intervention program, based on frailty phenotypes and their influencing factors, is informative and easy for both healthcare professionals and patients to learn and master.
- Focusing on the dialysis process, the multicomponent intervention improves adherence and safety to a greater extent in patients undergoing MHD.
- Multicomponent interventions enhance pre-frailty status, mitigate risk factors associated with frailty, and improve quality of life in pre-frail MHD patients.
- Collaboration between nurses and allied healthcare professionals can significantly contribute to frailty management in MHD patients.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

LQY and XZY designed the research study. LQY and AML performed the research. HLZ and LXY provided help and advice on the multi-component intervention programs. LQY and XZY analyzed the data. LQY wrote the first draft. HLZ, LXY, JC, FF, YZ, and JYL made significant contributions to interpretation of data for the work. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study adhered to the principles of the Helsinki Declaration and received approval from the Medical Ethics Committee of the First People's Hospital of Lianyungang (LYG1701-01-02), Jiangsu Province. The participants were informed of the purpose, significance, risks and procedure of the study before enrolling in the study. Participants were informed that they could withdraw from the study at any time without leading to any consequences. All participants were provided with written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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