Clinical Interventions in Aging

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CLINICAL TRIAL REPORT

Improving Lower Limb Function and Frailty in Frail Older Patients with Acute Myocardial Infarction After Percutaneous Coronary Intervention: A Randomized Controlled Study of Neuromuscular Electrical Stimulation

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Background: A global public health problem, frailty is closely associated with poor prognosis after percutaneous coronary intervention (PCI) in older patients with acute myocardial infarction (AMI). Although exercise intervention is the most commonly used method to reverse and alleviate frailty, its application is restricted in patients with acute myocardial infarction following PCI due to cardiovascular instability and autonomic imbalance. Consequently, there is a need for a new practical intervention to address frailty syndrome in these patients.

Purpose: This study aimed to investigate the effect of neuromuscular electrical stimulation in frail older AMI patients post-PCI.

Patients and Methods: A single-blind, randomized controlled trial was carried out in the Department of Cardiovascular Medicine from March to October 2023. A total of 100 eligible participants were randomly divided into two groups: experimental (n = 50) and control (n = 50) groups, respectively. Both groups received usual care. The experimental group underwent neuromuscular electrical stimulation (NMES) on bilateral quadriceps and gastrocnemius muscles for 30 minutes daily from day 1 to day 7 after surgery. The primary outcomes measured included the frailty score, lower limb muscle strength, and lower limb muscle quality. Secondary outcomes included the activities of daily living score, inflammatory markers, and length of hospital stay. All participants were included in an intention-to-treat analysis after the study ended.

Results: The frailty scores of the two groups exhibited a gradual decrease over time, and the scores of the experimental group were lower than those of the control group at 4 and 7 days after surgery ($P<0.001$). Concurrently, the lower limb muscle strength showed an increasing trend over the time in the experimental group and a decreasing trend in the control group, and the scores of the experimental group surpassed those of the control group ($p<0.001$). Moreover, a statistical difference was observed in the lower limb muscle mass across the groups after 7 days postoperatively compared with baseline on both sides ($p<0.05$).

Conclusion: Neuromuscular electrical stimulation has the potential to enhance lower limb function and alleviate frailty in elderly patients with acute myocardial infarction after PCI. These findings introduce a novel intervention approach for frailty management in the elderly population.

Keywords: acute myocardial infarction, older, frailty, neuromuscular electrical stimulation, PCI

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Introduction

Acute myocardial infarction (AMI) is a prevalent cardiovascular disease. The older population is particularly susceptible to a high incidence of myocardial infarction.[1] With the increase in the global aging population, the prevalence and mortality rate of AMI are increasing annually,[2] and AMI has become a major cause of death in humans. Percutaneous coronary intervention (PCI) is an effective method for treating AMI.[3] Frailty is a clinical illness characterized by an age-related decline in physiological reserve and destruction of homeostasis, resulting in increased frailty and a decreased ability to withstand stress, leading to various adverse health outcomes.[4] The occurrence of frailty in cardiac surgery patients is as high as 20% to 50% and is apparently greater than that in noncardiac surgery patients.[5] A meta-analysis revealed that the occurrence of frailty after PCI in AMI patients was 39%.[6] Hence, frailty is significantly related to poor prognosis after PCI in older AMI patients and increases the risk of vascular access complications, prolonged post-operative hospital stay, excessive bleeding, and death.[7] Therefore, strengthen the management of frailty in older AMI patients following PCI is essential for positive outcomes.

Frailty and cardiovascular disease share several commonalities. Research indicates that both diseases exhibit similar epidemiological and pathophysiological characteristics, with their incidence rising notably with age. Chronic inflammation plays a pivotal role in the pathogenesis of both conditions. Elevated inflammation levels contribute to the onset and progression of cardiovascular diseases, particularly atherosclerosis, by inducing vascular inflammation, endothelial dysfunction, and oxidative stress. Conversely, chronic inflammation-induced inflammatory aging exerts direct or indirect impacts on musculoskeletal, endocrine, cardiovascular, and hematological systems, contributing to the onset of frailty.[8] Not only the occurrence and development of cardiovascular disease and frailty promote each other, but also the two can influence each other. Frailty increases the fragility of the heart, weakens the compensatory ability of the heart, and increases the chance of adverse events. Simultaneously, cardiovascular disease exacerbates the occurrence and progression of frailty, leading to further decline in patients' functional capacity and worsening of the condition. Research indicates that frailty serves as a reliable predictor of mortality among patients undergoing coronary intervention. As frailty worsens, surgical complications increase, hospital stays lengthen, and the phenomenon correlates with age.[9] Frailty exhibits a strong correlation with in-hospital mortality, 1-month mortality, and extended hospitalization among individuals with acute coronary syndromes. Patients with frailty and concurrent medical conditions face elevated risks of mortality, recurrent myocardial infarction, revascularization, hospitalization, severe bleeding, and stroke.[10] Frailty and cardiovascular disease are interrelated. Hence, integrating frailty into cardiovascular practice is essential, and there is significant importance in endeavoring to address and prevent frailty syndrome within the context of cardiovascular disease.

Related guidelines and expert consensus state that exercise intervention is the most used interventions to reverse or alleviate frailty, and this intervention primarily includes resistance, aerobic, and balance exercises.[11,12] However, most AMI patients rest in bed after PCI, and the rate of participation and compliance with early postoperative exercise rehabilitation is not high.[13] Additionally, patients with post-PCI myocardial infarction and frailty cannot tolerate exercise interventions much due to the subsequent decline in physical function, exercise tolerance, and physical activity capacities. Early rehabilitation exercise training is done by bed exercises and is gradually transferred to sitting, standing, and walking by the bed.[14] Moreover, frail AMI patients after PCI develop hemodynamic instability and autonomic disorder,[15] thereby limiting early exercise interventions. Therefore, there is an urgent need for innovative and practical interventions to effectively improve or reverse frailty in such older patients with critical diseases.

A physiotherapy technique, neuromuscular electrical stimulation (NMES), involves stimulating the neuromuscular system with electric current pulses at various frequencies to induce muscle contraction, improve muscle strength and function, or treat neuromuscular system injuries.[16] It is a promising new training modality with the advantages of not requiring patient cooperation, being easy to perform in a hospital bed, being safe and non-invasive, easy to operate as well as affordable.[17] It has already been recognized as an alternative therapy for promoting exercise in critical patients.[18] Electrical stimulation can be applied directly to muscle fibers during NMES therapy to thicken, increase in size and weight, and enhance their oxygen metabolism and strength; it also improves local and lymphatic fluid circulation and accelerates the recovery of myofibrillar function.[19] The application of NMES in patients with cardiovascular disease is safe and effective. Sumin et al[20] utilized neuromuscular electrical stimulation in the early rehabilitation of patients with

complications following cardiovascular surgery. The findings indicated that NMES could effectively enhance knee extensor muscle strength in these patients. Tanaka et al[17] incorporated NMES therapy into early rehabilitation treatments for frail older patients with acute heart failure, and observed significant improvements in lower limb function. Bloeck et al[21] demonstrated that neuromuscular electrical stimulation is both safe and feasible for elderly patients with frailty, improving their lower limb strength and function. In addition, studies indicate that NMES can be safely performed in AMI patients immediately after cardiac surgery, and there is no evidence of unstable fluid dynamics.[15,22,23] Therefore, NMES training is suggested as a possible therapeutic option for cardiorespiratory rehabilitation and as an effective auxiliary treatment in frail patients with AMI.[24]

Thus, a randomized controlled trial was conducted to assess the efficacy of NMES in frail older patients with AMI following PCI by analyzing frailty scores, lower extremity muscle strength, lower extremity muscle mass, and other measures. This study aimed to provide a simple, inexpensive, safe, and feasible rehabilitation training therapy for frail older AMI patients post-PCI and impart a scientific reference for optimizing intervention protocols for frail older patients. We hypothesized that the intervention's effectiveness might increase its prospective clinical application value.

Materials and Methods

Participants

Inclusion and Exclusion Criteria

We included frail older patients who underwent emergency PCI in the Department of Cardiovascular Medicine from March to October 2023. The inclusion criteria were: 1. Patient's age ≥60 years; 2. Those with a confirmed diagnosis of AMI with stenting; and 3. Those with ≥5 points by Clinical Frailty Scale (CFS). The exclusion criteria were: 1. Patients contraindicated to neuromuscular stimulation (pacemaker or implantable defibrillator, severe cardiac arrhythmia, cardiac function class IV, dermatitis, skin damage or sensitivity changes); 2. Those with limb mutilation or metal prosthesis; 3. Patients with neuromuscular diseases (Duchenne's disease, Myasthenia Gravis, and Guillain-Barre syndrome), and; 4. Those who refused to participate or were mentally disturbed. The Department is the National Chest Pain Center, which includes two units of cardiovascular medicine and one unit of cardiology intensive care. Together, these units include 120–150 beds, 48–55 nurses, and 22–26 physicians. The trial protocol received approval from the Ethics Committee of the Affiliated Hospital of Southwest Medical University (KY2023032) and was conducted in accordance with the principles of the Declaration of Helsinki. The study was registered with the China Clinical Trial Registry (ChiCTR2300070846) and adhered to the recommendations of the Consolidated Standards for Reporting Trials (CONSORT 2010). Patients volunteered and signed informed consent forms, either by themselves or their guardians.

Sample Size Calculation

We determined our sample size using the sample content estimation method for comparing means of two independent samples ($n1 = n2 = 2[(\mu\alpha+\mu\beta)\sigma/\delta]^2$). Here, $U\alpha$ and $U\beta$ represent the corresponding U values for α (0.05) and β (0.2), with $U\alpha = 1.96$ and $U\beta = 0.84$. Based on prior studies on frailty,[25] the frailty score for the experimental group was 3.07±0.21, and for the control group, it was 3.23±0.26. Here, σ denotes the standard deviation of the frailty score, which is 0.26, and δ represents the difference between the average frailty scores of the experimental and control groups, with a value of 0.16. The final estimated sample size was 50 cases per group after it was determined that 41 patients should be included in each experimental and control group and that 20% of these were lost to interviews.

Study Design

Randomization and Masking

In this single-blind, randomized, controlled trial, random numbers and corresponding grouping information were generated with Excel 2019 (Microsoft Office, USA), random numbers ranging from 1 to 50 were allocated to the experimental group, while random numbers ranging from 51 to 100 were allocated to the control group. Randomization was carried out by a cardiovascular physician who was not a part of the intervention and study teams. The investigator placed random numbers and grouped information into numbered, opaque yellow sealed envelopes. Following patient enrollment, another investigator opened the envelopes in a sequence of serial numbers and assigned patients to the

appropriate group based on the numbers. The randomization assignment was kept confidential from all patients until the intervention started.

Blinding

We followed a single-blind procedure by blinding both the data collector and the statistical analyzer to prevent them from knowing the subjects' subgroups. Blindness was revealed upon the completion of the meticulously performed statistical analysis of the data, which was supervised by a quality control officer.

Interventions

Research indicates that patients with acute myocardial infarction in China typically require hospitalization for approximately 1 week.[26] Additionally, investigators were present in the ward and engaged in the study on a daily basis from March 27, 2023, to October 15, 2023, spanning 203 days during recruitment. Upon enrollment in the cardiovascular unit, patients received the study regimen daily from postoperative day 1 until postoperative day 7. The detailed scheme is outlined below:

The control group underwent cardiovascular PCI postoperative nursing routines, including: 1. Health education; 2. Psychological care; 3. Basic care; 4. Medication guidance; 5. Dietary recommendations; 6. Lifestyle interventions; and 7. Rehabilitation training (as per the Expert consensus on exercise rehabilitation after percutaneous coronary intervention).[14]

NMES therapy was administered to the experimental group, based on the control group, (referring to Clinical practice NMES guidelines in critically ill patients).[27] The specific methods were: 1. Stimulation of the following muscle groups: Quadriceps femoris (one electrode sheet was placed 5 cm distal to the inguinal fold, the other was placed 3 cm proximal to the upper patellar edge), and gastrocnemius (electrode sheet was placed 10 cm below the popliteal fossa at the belly of gastrocnemius muscle and 5 cm below the distal gastrocnemius insertion); 2. Limb position: the patient was lying supine with the knee joint supported at a 30~40° flexion angle (beneath the knee cushion). 3. Waveform: bipolar low-frequency PC; 4. Frequency: 30~50 Hz; 5. Pulse duration: 350~400 milliseconds; 6. Treatment duration: left and right quadriceps femoris and calf gastrocnemius every 30 min per day; 7. Working phase frequency: once a day for seven days postoperatively. Patients should be able to tolerate the output current's intensity, and the treatment should be terminated as soon as possible in case of any discomfort to the patient.

Outcome Measures

Baseline Indicators

Basic information, including age, sex, education level, smoking and drinking history, and history of hypertension and diabetes, was collected via a self-designed questionnaire.

Primary Outcomes

Clinical Frailty Scale (CFS)

Formulated by Rockwood, CFS is a multi-dimensional assessment tool.[28] The Association for Acute Cardiovascular Care recommends CFS as an effective tool to assess frailty at admission time for acute cardiovascular diseases. The scale is divided into nine continuity levels: 1 represents health, ≥5 represents frailty, and 7 depicts severe frailty. The higher continuity levels indicated the severity of the frailty. The Cronbach's α coefficient of the Clinical Frailty Scale was 0.86, which suggested good reliability and validity.

Lower Limb Muscle Strength

A hand-held muscle strength tester (microFET2, USA) was used to measure lower limb muscle strength. It is an objective and portable measurement device of muscle strength, which has been widely used. The patients were placed in the supine position with their ankle joint in a neutral position and their hip and knee joints extended by 0°. The distal end of the metatarsal joint was used to position the dynamometer to measure the strength of the ankle-toe flexor muscle. Moreover, the hip and knee joints were flexed at 90°, the contralateral hip joint was placed in a neutral position, and the dynamometer was placed proximal to the ankle joint to measure the knee extensor muscles' strength. After exerting the force for 2s, the patient reached the maximum contraction and held it for 3~5s. Each joint was measured thrice, at least 30s apart, and an average score was considered.

Lower Limb Muscle Mass

Calf circumference was used to measure lower limb muscle mass. Calf circumference is positively correlated with muscle mass and skeletal muscle mass index and is a simple and effective indicator of sarcopenia.[29] The inelastic tape was applied on the thickest area of the patient's calf gastrocnemius muscle and was wrapped horizontally. When the circumference was measured, the tape was near the skin, without any gaps or tension. Measurements were taken twice, and an average was taken to a precision of 0.1 cm.

Secondary Outcomes

Barthel Index (BI)

Developed by Mahoney et al, Barthel Index (BI) assesses the basic self-care ability of daily life activities.[30] The scale does not require assistance from others, with a total of 10 entries and 100 points. Moreover, 61 to 99 points indicate basic care in daily life; 41 to 60 scores state that assistance is needed for day-to-day life; 21 to 40 points suggest that existence is definitely dependent on others, and ≤20 score depicts an existence entirely dependent on others. The Cronbach's α coefficient of the Barthel Index Scale was 0.842, denoting good reliability and validity.

Inflammatory Markers

White blood cell, neutrophil, and lymphocyte counts were used as indicators of inflammation in frail patients. The patients' venous blood samples were obtained by routine laboratory testing methods.

Length of Hospital Stay

The data was collected by reviewing patients' medical records after discharge.

Data Collection

All baseline indicators were obtained from case files or face-to-face interviews after admission. While the length of hospitalization was obtained from the case files after discharge, the remaining outcome indicators were evaluated by trained professionals at baseline, four days, and seven days after the intervention.

Quality Control

A centralized training method was used to instruct researchers, outlining the study instruments and equipment, as well as the assessment scales and evaluation techniques, to minimize bias due to human error. Moreover, a standard training method was used to coach nurses in the Cardiology Department of the study unit to standardize the care of older AMI patients after PCI to improve the comparability of care between the groups.

Adverse Events and Treatment Programs

If a patient developed a serious adverse cardiovascular event during treatment, the treatment was terminated immediately, and physician care was required. If a patient developed a burning sensation on the skin during treatment, the skin condition was observed after treatment cessation, and a dermatologist was called for treatment if necessary.

Data Analysis

All the statistical analyses were performed using SPSS 26.0 software (IBM, Armonk, NY, USA). A significance level of $p<0.05$ was employed, and two-tailed tests were used when appropriate. Independent sample t tests were applied for normally distributed measurement data, Mann–Whitney *U*-tests were used for nonnormally distributed data, and χ^2 tests, along with Fisher's exact probability method, for comparing the count data between groups. Repeated-measures analysis of variance was performed on data with ≥ three measurements. Within-subjects effect tests were used to see if Mauchly's test of sphericity was satisfied; if not, we used the multivariate tests. Additionally, simple effect analyses were performed if there was an interaction effect in the statistical results. Since we used intention-to-treat (ITT) analysis, its sample size was calculated as 50 cases per group in randomized groups, while all missing values were calculated using the serial mean method for missing data.

Results

Recruitment of Subjects

A total of 291 AMI patients following PCI were admitted during the recruitment period. After the inclusion and exclusion criteria were screened, one hundred patients were randomly divided into experimental (n = 50) and control (n = 50) groups, respectively. One patient refused to continue treatment on day 2 due to psychological reasons, one patient refused day 4 therapy because of pain, and two patients discharged on days 5 and 6 were lost to follow-up, respectively. In the control group comprising 50 cases, one patient discharged on hospital day 6 was lost to follow-up (Figure 1).

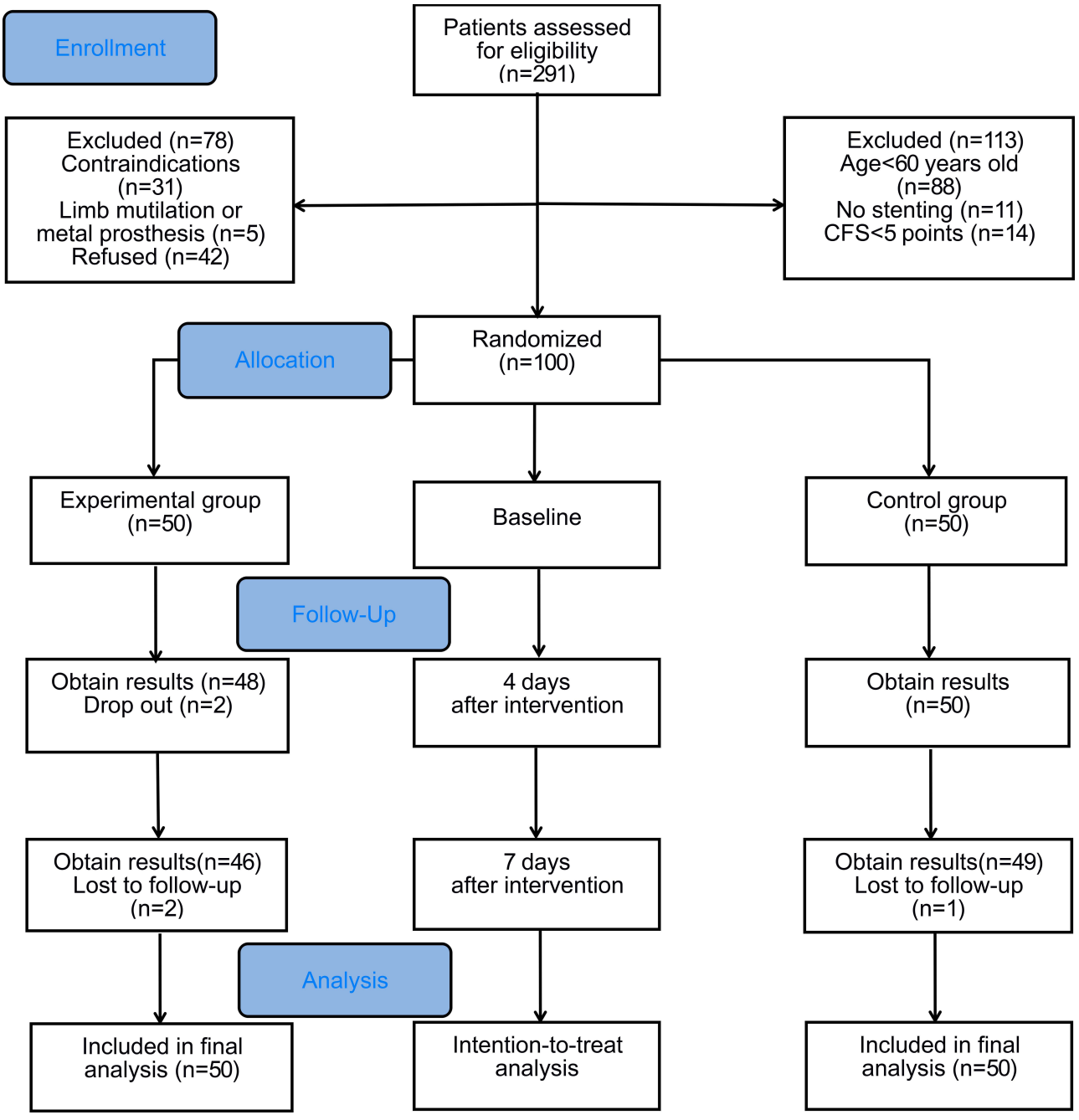

Figure 1 Study flow chart.

Baseline Characteristics of the Participants

Table 1 presents the baseline characteristics of the study participants. There were no significant differences between the groups in terms of age, sex, education level, marital status, smoking and drinking history, cardiac function classification, or history of hypertension and diabetes.

Table 1 Baseline Patient Characteristics

Demographic Characteristics	Experimental Group (n=50)	Control Group (n=50)	*P*-value	Statistic of Test
Age(year)	71.68±6.50	72.52±7.16	0.541	−0.614(t)
Height(m)	1.62±0.08	1.61±0.07	0.451	0.757(t)
Weight(kg)	61.72±10.44	59.45±11.25	0.298	1.046(t)
BMI (kg/m2)	23.54±3.37	23.00±3.79	0.453	0.754 (t)
Gender (%)			0.248	1.333 (χ^2)
Male	40 (80%)	35 (70%)		
Female	10 (20%)	15 (30%)		
Occupation (%)			0.134	4.017 (χ^2)
Peasantry	39 (78%)	30 (60%)		
Worker	1 (2%)	1 (2%)		
Retiree	10 (20%)	19 (38%)		
Insurance (%)			0.022	5.263 (χ^2)
Resident insurance	45 (90%)	36 (72%)		
Worker insurance	5 (10%)	14 (28%)		
Marriage (%)			0.497	1.398 (χ^2)
Married	45 (90%)	44 (88%)		
Divorced	0 (0%)	1 (2%)		
Widowed	5 (10%)	5 (10%)		
Residence (%)			0.171	1.871 (χ^2)
City	10 (20%)	16 (32%)		
Village	40 (80%)	34 (68%)		
Income (%)			0.429	−0.79(z)
<1000 dollar	32 (64%)	28 (56%)		
1001–3000 dollar	8 (16%)	9 (18%)		
3001–5000 dollar	9 (18%)	13 (26%)		
5001–10,000 dollar	1 (2%)	0 (0%)		
Education (%)			0.982	−0.022(z)
Illiteracy	11 (22%)	15 (30%)		
Primary school	28 (56%)	21 (42%)		
Junior high school	11 (22%)	11 (22%)		
Senior high school	0 (0%)	3 (6%)		
Smoke (%)			0.341	2.154 (χ^2)
Never	14 (28%)	21 (42%)		
Quit	10 (20%)	8 (16%)		
Smoking	26 (52%)	21 (42%)		
Drink (%)			0.570	1.123 (χ^2)
Never	21 (42%)	26 (52%)		
Quit	11 (22%)	8 (16%)		
Drinking	18 (36%)	16 (32%)		
Exercise (%)			0.322	2.269 (χ^2)
Never	2 (4%)	4 (8%)		
Sometimes	35 (70%)	28 (56%)		
Often	13 (26%)	18 (36%)		

(*Continued*)

Table 1 (Continued).

Demographic Characteristics	Experimental Group (n=50)	Control Group (n=50)	*P*-value	Statistic of Test
Heart function (%)			0.547	−0.602(z)
Level I	7 (14%)	9 (18%)		
Level II	28 (56%)	28 (56%)		
Level III	15 (30%)	13 (26%)		
Classification (%)			0.391	0.735 (χ^2)
STEMI	32 (64%)	36 (72%)		
NSTEMI	18 (36%)	14 (28%)		
Implant-position (%)			0.680	0.17 (χ^2)
LCA	30 (60%)	32 (64%)		
RCA	20 (40%)	18 (36%)		
Hypertension	26 (52%)	33 (66%)	0.155	2.026 (χ^2)
Diabetes	10 (20%)	13 (26%)	0.476	4.332 (χ^2)
CVD	3 (6%)	10 (20%)	0.037	4.332 (χ^2)
Varicosity	8 (16%)	4 (8%)	0.218	1.515 (χ^2)
DVT	1 (2%)	1 (2%)	1.000	0.000 (χ^2)

Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, Non-st elevation myocardial infarction; LCA, left coronary artery; RCA, right coronary artery; CVD, cerebrovascular disease; DVT, deep venous thrombosis.

Primary Outcomes

Comparison of Clinical Frailty Scale Scores Between the Two Groups

Repeated-measures analysis of variance revealed that the CFS scores of the two groups were significantly different regardless of the group, time, and interaction effects ($p<0.001$). Further simple effect analysis suggested that there was no significant difference in baseline CFS scores between the two groups ($p = 1.000$); the experimental group's scores were lower than those of the control group at 4 and 7 days postoperatively ($p<0.001$). Comparison in the group, the CFS scores of two patient groups with postoperative durations of 4 and 7 days were lower than the baseline scores ($p<0.05$) and showed a decreasing trend with time (Table 2).

Table 2 Primary Outcomes Between the Two Groups

Outcome Variables	Group	Baseline	Post 4 Days	Post 7 Days	F	P
CFS scores	Experimental group (n=50)	6.64±0.56	5.32±0.51[a]	4.24±0.52[ab]	377.416	<0.001
	Control group (n=50)	6.64±0.53	6.16±0.55[a]	5.60±0.57[ab]	75.224	<0.001
	F	0	62.635	155.615		
	P	1	<0.001	<0.001		
Left quadriceps strength	Experimental group (n=50)	6.53±1.08	7.82±1.54[a]	8.89±1.42[ab]	163.624	<0.001
	Control group (n=50)	6.92±1.06	6.54±1.20[a]	6.33±1.12[a]	12.129	<0.001
	F	3.319	24.535	99.856		
	P	0.072	<0.001	<0.001		
Right quadriceps strength	Experimental group (n=50)	6.67±1.39	7.62±1.74[a]	8.89±1.41[ab]	12.58	<0.001
	Control group (n=50)	7.09±1.25	6.48±1.30[a]	6.35±1.11[a]	18.513	<0.001
	F	2.492	13.683	100.874		
	P	0.118	<0.001	<0.001		

(*Continued*)

Table 2 (Continued).

Outcome Variables	Group	Baseline	Post 4 Days	Post 7 Days	F	P
Left gastrocnemius strength	Experimental group (n=50)	4.35±0.72	4.95±0.80[a]	5.72±0.82[ab]	100.021	<0.001
	Control group (n=50)	4.58±0.89	4.02±0.77[a]	3.77±0.59[ab]	50.895	<0.001
	F	2.007	34.973	186.077		
	P	0.16	<0.001	<0.001		
Right gastrocnemius strength	Experimental group (n=50)	4.46±0.60	5.21±0.80[a]	5.85±0.72[ab]	124.721	<0.001
	Control group (n=50)	4.71±0.78	4.00±0.80[a]	3.98±0.67[a]	65.752	<0.001
	F	3.146	56.901	180.676		
	P	0.079	<0.001	<0.001		
Left lower limb muscle mass	Experimental group (n=50)	31.29±2.73	31.34±2.65	31.57±2.53[ab]	4.729	0.011
	Control group (n=50)	30.84±2.73	30.92±2.72	30.76±2.84	1.58	0.211
	F	0.656	0.624	2.259		
	P	0.42	0.431	0.136		
Right lower limb muscle mass	Experimental group (n=50)	31.46±2.73	31.56±2.66	31.65±2.52	1.023	0.363
	Control group (n=50)	31.10±2.69	31.01±2.66	30.88±2.77	1.473	0.234
	F	0.445	1.061	2.089		
	P	0.506	0.305	0.152		

Notes: [a]Indicates comparison with baseline, $P<0.05$; [b]Indicates comparison with 4 days postoperatively, $P<0.05$; both comparisons are Bonferroni corrected. The main effect sizes are as follows, CFS scores: F(group)=70.583, $P<0.001$; F(time)=393.348, $P<0.001$; F(group×time) =59.292, $P<0.001$. Left quadriceps strength: F(group)=26.312, $P<0.001$; F(time)=53.661, $P<0.001$; F(group×time) =152.275, $P<0.001$. Right quadriceps strength: F(group)=17.986, $P<0.001$; F(time)=38.256, $P<0.001$; F(group×time) =139.119, $P<0.001$. Left gastrocnemius strength: F(group)=42.837, $P<0.001$; F(time)=7.747, $P<0.001$; F(group×time) =143.170, $P<0.001$. Right gastrocnemius strength: F(group)=54.953, $P<0.001$; F(time)=11.785, $P<0.001$; F(group×time) =178.687, $P<0.001$. Left lower limb muscle mass: F(group) =1.090, $P=0.299$; F(time)=1.125, $P=0.327$; F(group×time) =5.173, $P=0.006$. Right lower limb muscle mass: F(group)=1.124, $P=0.292$; F(time)=0.037, $P=0.964$; F(group×time) =2.459, $P=0.091$.

Comparison of Lower Limb Muscle Strength Between the Two Groups

Table 2 also showed that the strength of the quadriceps and gastrocnemius muscles on the left and right sides in the two groups was statistically significant in terms of intergroup, time, and interaction effects ($p<0.001$). Further simple effect analysis indicated that there was no significant difference in lower limb muscle strength between the two groups at baseline level ($p>0.05$). Moreover, the experimental group exhibited higher scores than the control group at 4 and 7 days postoperatively ($p<0.001$). The intra-group comparison revealed that the lower limb muscle strength at 4 and 7 days postoperatively was greater than the baseline muscle strength in the experimental group ($p<0.05$), while the control group's score was lower than the baseline score either at 4 or 7 days postoperatively. The lower limb muscle strength gradually increased in the experimental group and decreased in the control group over time.

Comparison of Lower Limb Muscle Mass Between the Two Groups

The repetitive-measures analysis of variance revealed no significant differences within the two groups of patients with left lower limb muscle mass according to the intergroup or time effects ($p>0.05$). However, the interaction effect reached statistical significance ($p = 0.006$). Additionally, there were no significant differences in right lower limb muscle mass between the two groups regarding the group, time, and interaction effects ($p>0.05$, Table 2). Further inter-group comparisons of their pre- and post-intervention differences were carried out following the statistical analysis strategy of randomized controlled studies. Table 3 shows that no statistical significance was observed in lower limb muscle mass across the groups after 4 days postoperatively compared with baseline, on either left or right sides ($p>0.05$); but a statistical difference was noticed in the lower limb muscle mass across the groups after 7 days postoperatively compared with baseline on both sides ($p<0.05$).

Secondary Outcomes

Comparison of the Self-Care Ability of Daily Living Between the Two Groups

Table 4 shows that the BI scores of the two groups were statistically significant in terms of between-group, time, and interaction effects ($p<0.001$). Moreover, no statistical significance was observed in the baseline intergroup comparison

Table 3 Change of Scores in Lower Limb Muscle Mass Between the Two Groups

Outcome Variables		Experimental Group (n=50)	Control Group (n=50)	t	P
Lower limb muscle mass	Left baseline	31.29±2.73	30.84±2.73	0.81	0.42
	Left change1	0.06±0.67	0.08±0.68	−0.133	0.895
	Left change2	0.28±0.78	−0.08±0.63	2.584	0.011
	Right baseline	31.46±2.73	31.10±2.70	0.667	0.506
	Right change1	0.10±0.84	−0.09±0.66	1.227	0.223
	Right change2	0.19±1.02	−0.22±0.80	2.204	0.03

Notes: Change 1 indicates the value of change from baseline at 4 days postoperatively; change 2 indicates the value of change from baseline at 7 days postoperatively.

Table 4 Secondary Outcomes Between the Two Groups

Outcome Variables	Group	Baseline	Post 4 Days	Post 7 days	F	P
Barthle scores	Experimental group (n=50)	20.90±2.19	59.30±12.98[a]	84.42±10.56[ab]	679.112	<0.001
	Control group (n=50)	20.90±1.94	39.70±10.57[a]	51.10±12.59[ab]	163.618	<0.001
	F	0	68.595	181.619	—	—
	P	1	<0.001	<0.001	—	—
Leucocyte count	Experimental group (n=50)	10.37±3.51	7.47±1.80	6.93±1.85	—	—
	Control group (n=50)	9.77±3.60	7.18±2.61	6.96±2.30	—	—
Neutrophil count	Experimental group (n=50)	8.25±3.32	4.91±1.52	4.44±1.45	—	—
	Control group (n=50)	7.80±3.52	4.90±2.36	4.63±2.01	—	—
Lymphocyte count	Experimental group (n=50)	1.46±0.75	1.59±0.57	1.60±0.54	—	—
	Control group (n=50)	1.39±0.77	1.44±0.56	1.46±0.54	—	—

Notes: [a]Indicates comparison with baseline, $P<0.05$; [b]Indicates comparison with 4 days postoperatively, $P<0.05$; both comparisons are Bonferroni corrected. The main effect sizes are as follows, Barthle scores: F(group)=70.583, $P<0.001$; F(time)=393.348, $P<0.001$; F(group×time)=59.292, $P<0.001$. Leucocyte count: F(group)=0.392, $P=0.532$; F(time)=60.522, $P<0.001$; F(group×time)=0.908, $P=0.407$. Neutrophil count: F(group)=0.048, $P=0.828$; F(time)=70.687, $P<0.001$; F(group×time)=0.696, $P=0.501$. Lymphocyte count: F(group)=1.256, $P=0.265$; F(time)=1.290, $P=0.280$; F(group×time)=0.188, $P=0.829$.

(p = 1.000). Additionally, the experimental group scored higher than the control group in both the 4-and 7-day postoperative intergroup comparisons ($p<0.001$). The intra-group comparison results suggested that the BI scores of both groups at 4 and 7 days postoperatively were higher than the baseline scores ($p<0.05$), which showed a gradual incremental trend over time.

Comparison of Inflammatory Indicators Between the Two Groups

Repeated measures of variance's results showed that no statistical significance was noticed in the between-group and interaction effects for white blood cell and neutrophil counts in both groups ($p>0.05$). However, the time effect reached statistical significance ($p<0.001$). Lymphocyte count was not statistically significant in either group concerning the between-group, time, and interaction effects ($p>0.05$, Table 4). Additional intergroup comparisons of their pre-and post-intervention differences were performed, and the differences were not significant ($p>0.05$, Table 5).

Comparison of the Length of Stay Between the Two Groups

According to the Mann–Whitney U-test, no significant differences were observed in the length of stay between the two groups (p = 0.277, Z =−1.088). The duration of hospitalization was 10 (8,11)d in the experimental group and 10.5 (8,12)d in the control group.

Adverse Events

No serious cardiovascular or NMES adverse effects occurred during the study period.

Table 5 Change of Scores in Inflammation Indicators Between the Two Groups

Outcome Variables		Experimental Group (n=50)	Control Group (n=50)	t	P
Inflammation indicators	Leucocyte baseline	10.37±3.51	9.77±3.60	0.835	0.406
	Leucocyte change1	−2.89±2.95	−2.60±2.74	−0.521	0.603
	Leucocyte change2	−3.44±2.92	−2.82±2.74	−1.098	0.275
	Neutrophil baseline	8.25±3.32	7.80±3.52	0.654	0.514
	Neutrophil change1	−3.35±2.95	−2.90±2.84	−0.762	0.448
	Neutrophil change2	−3.81±2.89	−3.17±2.95	−1.089	0.279
	Lymphocyte baseline	1.46±0.75	1.39±0.77	0.431	0.668
	Lymphocyte change1	0.13±0.59	0.05±0.80	0.561	0.576
	Lymphocyte change2	0.14±0.64	0.06±0.63	0.608	0.545

Notes: Change 1 indicates the value of change from baseline at 4 days postoperatively; change 2 indicates the value of change from baseline at 7 days postoperatively.

Discussion

As the population ages, the management of frailty is becoming a growing concern. Although studies have shown that exercise intervention can effectively reverse or alleviate frailty,[11,12] it is severely limited in frail older AMI patients following PCI. In this study, we explored the efficacy of NMES in frail older AMI patients after PCI using a randomized controlled trial. It was found that after seven days of intervention, the difference between the NMES groups regarding the CFS scores, lower limb muscle strength, and BI scores was statistically significant on days 4 and 7 postoperatively, while the difference in lower limb muscle mass was statistically significant on postoperative day 7. It is suggested that NMES can improve frailty, lower limb function and the ability to self-care in daily life activities in frail older AMI patients after PCI. This study solves the bottleneck problem of frail management in older patients for acute myocardial infarction after PCI. It provides a new option for the management of frailty in older people.

To the best of our knowledge, this study is the first to explore the effectiveness of NMES in improving the frailty of older AMI patients following PCI. Several studies have demonstrated the effectiveness of NMES in preventing ICU-acquired frailty,[31,32] but very few studies, except Japanese and German studies, have been undertaken in the field of geriatric frailty.[17,21,33] However, these studies did not include frailty as an outcome indicator, and lower limb function was used as the primary outcome. This might be because sarcopenia is a significant factor causing frailty, and changes in muscle-related markers might effectively indicate the development of frailty syndromes.[34] Although there may be an association between sarcopenia and frailty,[35] sarcopenia is characterized by a loss of skeletal muscle and muscle mass, whereas frailty comprises a broader range of variables and clinical manifestations and develops due to more complex mechanisms than sarcopenia alone.[36] Therefore, using the frailty score as the primary outcome indicator in this study is both innovative and meaningful, and our results might provide direct evidence that NMES improves frailty in older patients. However, the CFS used in this study requires a high degree of professionalism and subjectivity on the part of the assessor. Therefore, future studies might incorporate more objective frailty assessment tools to enhance the reliability of the findings.

Like in previous studies, we found that NMES improved lower limb muscle strength in frail older AMI patients after PCI.[21,37] The underlying mechanism may be through the enhancement of skeletal muscle strength and endurance by NMES, which inhibits muscle protein catabolism and promotes muscle protein synthesis.[38] It might also improve the lower limb muscle strength by increasing the satellite cells' division ability.[39] Moreover, the improvement of lower limb muscle strength by NMES is closely related to the brain's plasticity, in which the brain regions' electrical activity is enhanced with increased electrical stimulation intensity.[40] It is surprising that seven consecutive days of NMES intervention is sufficient to make a difference in frail older patients, which highlights not only the great potential for improving lower limb muscle strength in frail older patients but also the time efficiency of NMES. As a relatively mature, safe, simple, and inexpensive rehabilitation method, NMES has been widely used in lower limb muscle strength rehabilitation in older people to improve lower limb muscle strength. On the one hand, NMES can promote the blood circulation of all lower limbs and improve their function. On

the other hand, it may increase patients' comfort after PCI for acute myocardial infarction and improve the patients' experience of medical treatment, which is worth promoting in clinical application.

Notably, our results showed that NMES improved lower limb muscle mass in frail older AMI patients after PCI. This is due to the positive correlation between muscle mass and muscle strength.[41] NMES can enhance muscle mass by modifying muscle-specific transcriptional mechanisms.[42] Moreover, NMES boosts IGF-1 expression and its downstream pathway while reducing the expression of the muscle atrophy-associated ubiquitin ligases MuRF1 and atrogin1, thereby combating muscle atrophy in patients.[43] However, our results were inconsistent with those of Homma et al.[44] This may be because the frequency and intensity of electrical stimulation in the study by Homma et al were low and because the exercise intensity was lower than that of resistance training, which cannot serve as an adequate load to alter muscle mass. Since the muscle mass increased after the muscle strength improved and the difference had not yet appeared at the time of measurement.[45] This explains why there was no difference in muscle mass changes between the two groups after 4 days of intervention, whereas a statistically significant difference was seen only after 7 days of intervention in our results. Hence, the optimal frequency and duration of NMES therapy should be explored in the future to improve lower limb function in frail older patients.

Improvements in the lower limb muscle status are crucial are essential for mobility, exercise, self-care in daily life, and avoiding other factors associated with poor prognoses. In this study, NMES was used to improve and promote lower limb function in frail older AMI patients following PCI, thereby improving the patient's ability to self-care in daily life and enhancing their quality of life.

However, the present study had a few limitations. Firstly, this was a single-center study conducted in Luzhou, China. Thus, the results may not be generalizable to other countries or regions because of the small sample size, and further validation is needed. Secondly, the study's intervention time of seven days was too short. Therefore, the accurate effects of NMES on inflammation indicators and length of stay could not be gauged. Hence, the clinical intervention time can be extended, or animal experiments can be conducted in the future to observe the efficacy and mechanism of action. Thirdly, the study was not blinded to the participants, so contamination among them could not be avoided, and a multicenter study may be conducted in the future to reduce bias. Fourthly, because of the limited funding and experimental conditions, some outcome indicators could not be measured precisely, such as the measurement of lower limbs' muscle mass, which can be measured by surface electromyography in the future to improve the reliability and persuasiveness of our results.

Conclusion

In this study, we found that NMES can improve the frailty, lower limb function, and self-care ability for daily life activities in frail older AMI patients after PCI. Our results might provide appropriate intervention strategies for managing frailty in older AMI patients following PCI.

Patient Consent Statement

The patients volunteered to participate and signed an informed consent form either by themselves or their guardians.

Data Sharing Statement

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request. Please send your request for original data to the e-mail address of Professor Shengmin Guo at 2930773281@qq.com. No data other than those contained in the manuscript were shared.

Ethics Approval Statement

The trial protocol received approval from the Ethics Committee of the Affiliated Hospital of Southwest Medical University (KY2023032) and was conducted in accordance with the principles of the Declaration of Helsinki. The study was registered with the China Clinical Trial Registry (ChiCTR2300070846) and adhered to the recommendations of the Consolidated Standards for Reporting Trials (CONSORT 2010).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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