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The efficacy and safety of fecal microbiota transplantation in the treatment of sarcopenia: a retrospective study

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Abstract

Background Sarcopenia, a prevalent geriatric syndrome, is influenced by factors such as inflammation, immune deficiency, and oxidative stress. In elderly individuals, alterations in the microbiome, including reduced biodiversity and functional changes, significantly contribute to the progression of the disease. Targeting the gut-muscle axis has emerged as a promising therapeutic strategy to mitigate age-related muscle atrophy and dysfunction.

Methods This study employed fecal microbiota transplantation (FMT) to restore intestinal homeostasis in patients with sarcopenia. Muscle mass was measured using bioelectrical impedance analysis, while muscle function was assessed through grip strength and the five-time sit-to-stand test. Inflammatory markers, including tumor necrosis factor- α (TNF- α) and C-reactive protein (CRP), were also analyzed. Eighty-seven patients received resistance training (RT) treatment, while eighty-five patients received FMT combined with RT treatment, with a follow-up period of 24 weeks.

Results After 24 weeks, the resistance training (RT) group showed a partial remission (PR) rate of 54.7% and a complete remission (CR) rate of 32.4%. The FMT plus RT group demonstrated a PR rate of 66.5% and a CR rate of 46.7%. Significant improvements induced by FMT treatment were observed in clinical markers of muscle mass, function, and inflammation.

Conclusions These results underscore the promise of microbial-based therapies, including fecal microbiota transplantation (FMT), as groundbreaking strategies for addressing sarcopenia. The research indicates that integrating FMT with resistance training could improve muscle mass and function while alleviating inflammation in sarcopenia patients, presenting a hopeful avenue for effective management of the condition

Keywords Sarcopenia, Resistance training, Fecal microbiota transplantation, Microbiota

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Introduction

Sarcopenia, a clinical syndrome closely linked to aging, is characterized by a decline in skeletal muscle mass, reduced muscle strength, and/or impaired physical function [1–4]. With the global aging population increasing rapidly, sarcopenia has become a critical public health concern. The pathogenesis of sarcopenia is multifactorial, involving physical inactivity, hormonal changes, and vitamin D deficiency as significant risk factors. Age-related mechanisms such as disrupted muscle protein metabolism, neuromuscular degeneration, chronic inflammation, and oxidative stress also play critical roles in its progression [5, 6]. Current treatments for sarcopenia, including nutritional supplementation, exercise therapy, and pharmacological interventions, face significant challenges, such as suboptimal effectiveness, poor patient adherence, and limited availability of effective drugs. Recent research highlights a strong link between the gut microbiome and sarcopenia, particularly in the aging process [7, 8]. In adults, *Bacteroides* and *Firmicutes* dominate this ecosystem. These microbes are essential for sustaining physiological homeostasis and overall health. However, aging leads to changes in the composition, diversity, and function of the gut microbiota [9]. Notable shifts include a reduction in beneficial bacteria, rearrangements in the proportions of *Bacteroidetes* and *Firmicutes*, and increased individual variability. In older adults, these microbial alterations are linked to muscle mass and frailty, with higher microbial diversity correlating with better muscle mass [10]. Therefore, modulating the gut microbiota has emerged as a potential therapeutic strategy. Current approaches to modulating gut microbiota include probiotics, prebiotics, and fecal microbiota transplantation (FMT).

FMT involves the minimally processed transfer of fecal matter from a healthy donor to the intestinal tract of a recipient, with the goal of reestablishing a balanced gut microbial community and addressing conditions linked to gut microbiome imbalances [11, 12]. The gut microbiota, which includes a diverse array of microorganisms such as bacteria, viruses, fungi, protozoa, and archaea, is integral to maintaining human health and is implicated in various diseases. When the equilibrium of the gut microbiota is disturbed, it can result in dysbiosis, a condition associated with numerous ailments including constipation, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), colorectal cancer, metabolic syndrome, and autism [13–16]. Presently, FMT is recognized as a standard treatment for recurrent *Clostridium difficile* infection (rCDI) and is endorsed by international medical guidelines [17]. Current studies have found that FMT demonstrates significant therapeutic effects on gastrointestinal disorders such as chronic constipation, IBD, IBS and chronic diarrhea [18, 19]. Additionally, it has

shown certain efficacy in treating autism spectrum disorder with gastrointestinal symptoms, Parkinson's disease, and other systemic diseases [20, 21]. In this context, FMT has emerged as a promising approach to restore balance in the intestinal microbiota, with the goal of correcting microbial dysbiosis and potentially enhancing muscle mass and function. Studies in mouse models have demonstrated that FMT can alleviate aging-associated sarcopenia; however, no clinical studies have yet investigated the therapeutic potential of FMT for sarcopenia in humans. This clinical study investigates the efficacy of FMT in treating sarcopenia, exploring the relationship between gut microbiota and muscle health. The findings aim to provide insights into the role of gut-microbiota modulation and pave the way for novel therapeutic approaches to combat sarcopenia.

Methods and materials

Patient and data collection

This study is part of the research registered under the ClinicalTrials.gov identifier NCT06208930, with the registration date of January 7, 2024. The initial definition of sarcopenia was merely based on the reduction of muscle mass and quantity. Current research places greater emphasis on the importance of muscle strength, as well as the decline in physical function resulting from the decrease in muscle mass. Bioelectrical impedance analysis (BIA) technology is non-invasive, inexpensive, easy to operate, portable, and provides rich functional information. In recent years, it has been frequently used for large-scale population screening. BIA mainly collects and measures the changes in the impedance of tissue cells through bioelectrical sensors, and calculates the individual's fat volume and total body muscle mass. This study is a retrospective study. 172 sarcopenia patients who received FMT therapy at Shanghai Tenth People's Hospital between September 2022 and March 2024 were recruited. Inclusion criteria included individuals (a) middle-aged and elderly people aged over 60 years; (b) low level of muscle mass index (measured by bioelectrical impedance analysis, with the relative skeletal muscle mass index of the limbs (SMI) decreased to less than 7 kg/m² for men and less than 5.7 kg/m² for women); (c) having not taken antibiotics, probiotics, and other medications that may affect the gut microbiota or muscle function within nearly three months; (d) being able to cooperate and accept the implantation of a naso-jejunal tube. (e) Maintain a regular dietary pattern without any special dietary habits, and ensure that eating habits remain consistent before and after enrollment; (f) Engage in normal daily physical activity, with minimal variation in exercise levels before and after enrollment. Fecal samples were collected before and after FMT treatment, following sterile procedure and stored at low temperature.

Donor recruitment. The selection of unrelated donors adhered to the following criteria: (1) individuals aged between 18 and 30 years; (2) a Body Mass Index (BMI) ranging from 18 to 25 kg/m²; (3) absence of any pathological indications during physical assessments; (4) no past or recent occurrences of infectious diseases, nor gastrointestinal, metabolic, neurological, or other systemic conditions; (5) no recent consumption of medications known to adversely affect gut microbiota composition; (6) maintenance of a regular lifestyle, adherence to a healthy diet, engagement in suitable physical activity, harmonious family relationships, and abstention from smoking and alcohol consumption; (7) successful completion of blood and stool examinations 4 weeks prior to donation, encompassing standard blood and stool analyses as well as screenings for potential pathogens or infectious diseases. All our donors fulfilled these stipulated requirements. The detailed characteristics of donor subjects used in this study are presented in Table 1.

Recipient preparation. Before the FMT treatment was administered to patients, there were specific requirements and preparatory measures. The patients' vital signs had to be normal, and they should not have fever, severe infection, sepsis, systemic inflammatory response syndrome (SIRS), or other inflammatory conditions. For those patients with sarcopenia, antibiotic preparation (oral vancomycin, 500 mg, twice a day) was provided for six consecutive days. Then, a naso-jejunal tube was inserted into the proximal part of the patient's jejunum, and the position of this tube was confirmed by abdominal radiography. Subsequently, the donor fecal microbiota was infused through the naso-jejunal tube for six consecutive days. During the FMT treatment, antibiotics, hormones, and immunosuppressants were generally not recommended.

Preparation of FMT. The donor needs to defecate in a standard sampling room to collect a stool sample. A minimum sample weight of 100 g must be collected once into a pre-sterilized disposable specimen container using

aseptic technique. Upon collection, record exact mass of sample, transport to a disposable sample bucket in biological safety cabinet, and is immediately loaded into the laboratory preparation process. The sample bucket is installed in the automated fecal bacteria separation system, adding 0.9% NACI solution at 1:5 w/v ratio (e.g., 100 g sample + 500mL NACI solution). After stirring, mixing and filtering, it is automatically divided into disposable sterile centrifugal tubes. The liquid bacteria should be added with sterile glycerin and maintained at a final concentration of 10% glycerin, vortex mixed and stored frozen at -20 °C for 1 to 4 weeks for use. All containers in contact with samples are standardized disposable medical consumables. After the preparation process, clean and sterilize the sufaces of equipment and table promptly to avoid cross-contamination.

DNA extraction and 16 S rRNA gene sequencing. Microbial genomic DNA was extracted from fecal samples using the PowerMax Extraction Kit (Omega Bio-tek, Norcross, GA, USA) following the manufacturer's protocol. DNA quantification was then carried out using a NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). To amplify the 16 S rRNA V4 region, the universal primers 515 F (5'-GTGY-CAGCMGCCGCGGTAA-3') and 806R (5'-GGACTAC-NVGGGTWCTAAT-3') were used in a Polymerase Chain Reaction (PCR). The PCR reactions were set up in a 50 µL system with an initial denaturation at 98 °C for 30 s, followed by 25 cycles of denaturation at 98 °C for 15 s, annealing at 58 °C for 15 s, and extension at 72 °C for 15 s, concluding with a final extension at 72 °C for 1 min. The PCR products were purified using AMPure XP Beads (Beckman Coulter, Indianapolis, IN, USA), and the DNA concentration was measured using the Qubit dsDNA HS Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA). The fragment lengths of the PCR products were confirmed by gel electrophoresis. The prepared DNA libraries underwent sequencing on an Illumina NovaSeq 6000 platform (paired-end, 2×150 bp)

Table 1 The detailed characteristics of donor subjects used in this study

Donor ID	Sex	Age (Years)	BMI (kg/m ²)	Weekly Moderate-Intensity Exercise (minutes)	History of Antibiotic Use	Dietary Pattern
1	Female	22	19.56	162	No history of antibiotic use	Primarily consisting of fruits, vegetables, cereals, and dairy products
2	Female	24	19.27	156	No history of antibiotic use	Primarily consisting of meat, legumes, cereals, and vegetables
3	Female	23	20.17	169	No history of antibiotic use	Primarily consisting of cereals, vegetables, fruits, and meat
4	Male	25	21.60	171	No history of antibiotic use	Primarily consisting of cereals, vegetables, fruits and meat
5	Male	25	20.57	158	No history of antibiotic use	Primarily consisting of cereal grains, vegetables, fruits, and eggs
6	Male	23	22.84	167	No history of antibiotic use	Primarily consisting of cereal grains, vegetables, fruits, and eggs

after quality analysis was conducted at Shanghai Biotechan Pharmaceuticals Co., Ltd (Shanghai, China).

Data processing, analysis and visualization. Qiime2 version 2023.2.0 was employed to carry out DADA2 processing of the raw sequencing data. Initially, data underwent quality filtering to remove adapter and barcode sequences, and trimming to an appropriate length to remove sequences with an average quality score below 25. Sequences were then dereplicated, evaluated for sequence variants, merged, and subjected to chimera checking through a standard DADA2 procedure. Filtered representative sequences and biom-formatted tables were subsequently assigned with the silva v138.1 database. The resulting table and taxonomy artifacts were exported as a biom table and text file, respectively, for subsequent analyses following the addition of taxa data to the biom-formatted ASV table.

All alpha-diversity and beta-diversity indexes were computed and visualized using the “microeco” package (v0.15.0). The Principal Component Analysis (PCA), Principal Coordinate Analysis (PCoA), and Non-Metric Multidimensional Scaling (NMDS) plots based on Jaccard and Unweighted distances, the taxonomic composition bar plot, the feature abundance box plot, the Venn plot, and the heatmap plot were also generated by the “microeco” package. As the microbiota was presented in relative abundance, Linear Discriminant Analysis (LDA) effect size (LEfSe) analysis was employed to compare differences in microbiota composition. After setting the alpha value to 0.01 and the LDA score threshold to 4, the LEfSe bar plot and corresponding cladogram were drawn using the “microeco” package. The co-occurrence network was calculated by the “microeco” packaged using Spearman analysis to compute correlation coefficients, and P-value threshold was set to 0.01, while the coefficient threshold was automatically optimized. The cluster_fast_greedy method was then employed for network clustering and visualization was conducted using Gephi (v0.10.1). The Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUST2)

(v2.5.1) workflow was applied for the prediction of metagenome functions of microbiota, and the functional pathways were annotated by Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Statistical analysis. Chi-square test was used to compare the binary outcomes (partial response rate and complete response rate), and the Odds Ratio (OR) and 95% confidence interval (Mantel-Haenszel method) were reported. The proportions and their confidence intervals were calculated using the Wilson Score method to provide a quantification of the accuracy of the estimates. To assess the independent contribution of microbial changes to muscle mass, a multiple linear regression model was used to adjust for potential confounders, with results reported as regression coefficients (β) and their 95% confidence intervals.

In the microbiota analysis, differences in alpha diversity indices were assessed using the Kruskal–Wallis test. For the LEfSe analysis, differences in the abundance of characteristic taxa between the two groups were also evaluated using the Kruskal–Wallis test. Correlations between microbial abundance and clinical parameters were assessed using Pearson correlation analysis. Differences in clinical characteristics before and after FMT were examined using the Kruskal–Wallis test. Correlations among clinical features were calculated using Spearman correlation analysis, with the correlation coefficient (ρ) reported to indicate the strength and direction of associations. All P-values were corrected by the Benjamini-Hochberg method to reduce false positives caused by multiple comparisons. All statistical analyses were conducted using R (version 4.3.1), and a P-value < 0.05 was considered statistically significant.

Results

The safety of FMT for sarcopenia patients

After the intervention treatment, patients in both the FMT + RT group and the RT group were followed up during the treatment period and at the 4th week, 12th week, and 24th week after the treatment. The FMT + RT group had more adverse reaction events than the RT group, mainly including adverse reaction events such as abdominal pain, abdominal distension, and fatigue. However, most of these adverse reactions could relieve themselves upon clinical observation, and a small number of patients could be relieved after receiving symptomatic treatment with medications. No serious adverse reaction events were found (Table 2).

The adverse reactions observed in the FMT combined with resistance training (RT) group during the study, such as abdominal pain, abdominal distension, and fatigue, were as follows: Two patients in the FMT + RT group experienced persistent dull pain and discomfort, which was relieved after taking the antispasmodic drug

Table 2 Adverse reactions during treatment and follow - up after treatment in the FMT + RT group and the RT group

	FMT + RT(N = 85)	RT(N = 87)	P value
Abdominal pain	8(9.4%)	3(3.4%)	0.209
Abdominal distension	9(10.6%)	2(2.3%)	0.425
Fever	4(4.7%)	2(2.3%)	0.567
Fatigue	11(12.9%)	6(6.9%)	0.074
Diarrhea	7(8.2%)	3(3.4%)	0.354
Chest pain	3(3.5%)	2(2.3%)	0.144
Palpitations	3(3.5%)	3(3.4%)	0.545
Nausea	2(2.3%)	1(1.1%)	0.277
Vomit	4(4.7%)	0(0)	0.524
Muscle fatigue	9(10.6%)	11(12.6%)	0.125

pinaverium bromide. Secondly, one patient in each group had a fever during the treatment period, with a body temperature of 37.5°C-37.8°C, which was considered to be caused by a cold. They were given antipyretic symptomatic treatment and recovered. Additionally, two patients in this group experienced mild diarrhea after FMT, with 2–3 loose stools. One was given electrolyte supplementation, and the other was treated with montmorillonite powder, both of which were relieved. Post-transplant fatigue may be related to the immune regulation caused by FMT or the physical exertion of RT, and usually gradually subsides as the body adapts. Most adverse reactions resolved spontaneously within a few hours to several days during or after the treatment without the need for special intervention. In addition, we also conducted a long-term follow-up for half a year. In the FMT + RT group, three patients experienced diarrhea, with 1 to 3 episodes per day. In the RT group, one patient had diarrhea, which might be caused by getting cold or consuming unclean food. In both the FMT + RT group and the RT group, two patients in each group had a fever, with a body temperature of 37.5°C, which was likely related to a cold. These symptoms were relieved spontaneously after taking oral medications for symptomatic treatment.

FMT demonstrates a substantial enhancement in the treatment efficacy for sarcopenia patients

A total of 321 patients diagnosed with sarcopenia were prospectively enrolled at Shanghai Tenth People’s Hospital, affiliated with Tongji University, between September 2022 and March 2024. Of these, 172 met the inclusion criteria and were subsequently divided into two intervention groups. In the resistance training (RT) group ($n=87$), patients participated in a structured RT-based exercise program, with a frequency of 2–3 sessions per week, each lasting ≥ 30 min over a minimum duration of 8 weeks. The remaining 85 patients were assigned to the combined FMT and resistance training (FMT + RT) group (Fig. 1).

The ages of the two groups before treatment and various indexes related to sarcopenia are shown in Table 3, and no significant differences were found. Participants were followed longitudinally at baseline and at 4, 12, and 24 weeks post-intervention. Key outcomes included adverse events observed during and after the intervention period and measures of clinical efficacy. Primary endpoints comprised appendicular skeletal muscle mass index (ASMI), the SARC-F questionnaire (evaluating strength, assistance with walking, rising from a chair, climbing stairs, and falls; scores ≥ 4 indicative of sarcopenia), bioelectrical impedance analysis (BIA; thresholds for reduced muscle mass defined as <7.0 kg/m² in men and <5.7 kg/m² in women), handgrip strength (HS;

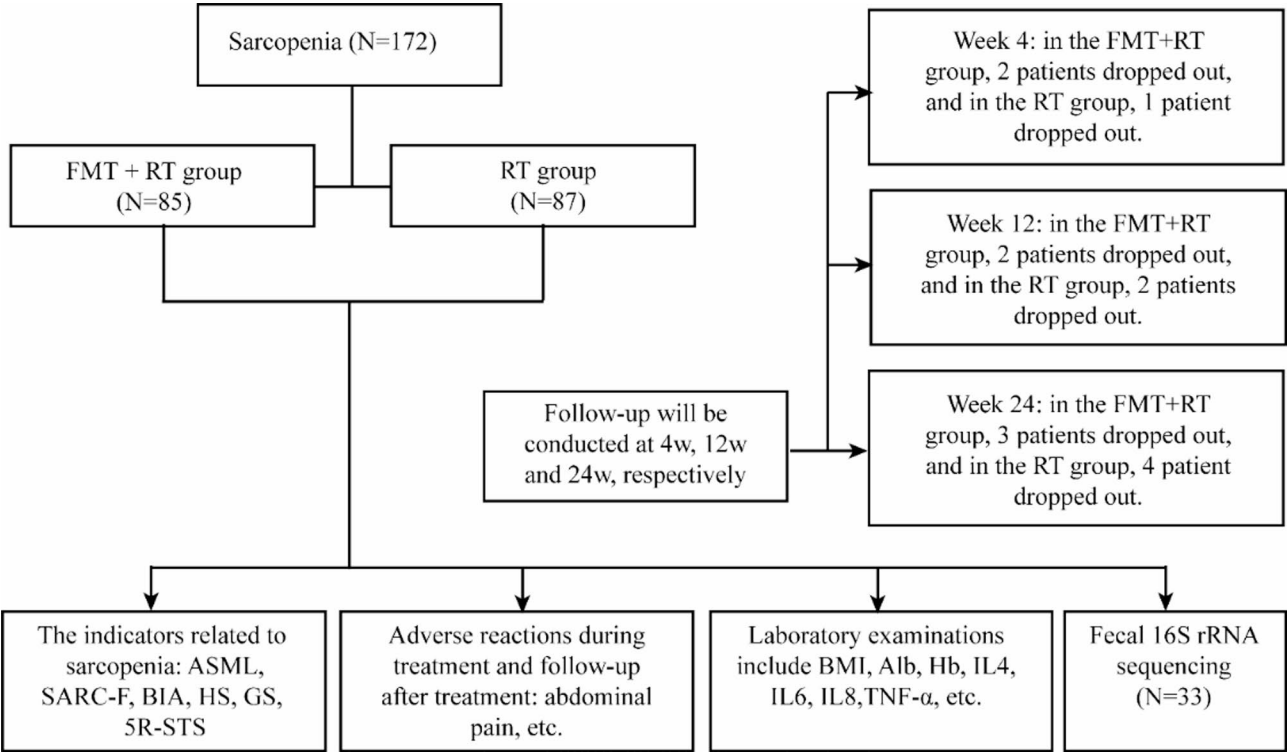


Fig. 1 Study design of FMT combined with resistance training (RT) for treating sarcopenia

Table 3 Baseline data of patients in the two groups

	FMT + RT	RT	P value
Age	64.3 ± 7.6	65.1 ± 7.1	>0.05
Female	45(52.9%)	38(43.7%)	
BMI(kg/M2)	15.8 ± 2.1	16.2 ± 2.2	>0.05
SARC-F	5.71 ± 1.45	5.77 ± 1.51	>0.05
ASMI	5.56 ± 1.23	5.69 ± 0.51	>0.05
BIA (kg/m2)	5.82 ± 0.88	5.86 ± 0.82	>0.05
HS(Kg)	20.6 ± 2.4	19.3 ± 2.6	>0.05
GS(m/s)	0.87 ± 0.23	0.79 ± 0.34	>0.05
5R-ST5	45 ± 8.9	47 ± 7.8	>0.05

SARC-F: the sarcopenia five-item questionnaire. SARC-F score ≥ 4 indicates a positive screening result. ASMI: appendicular skeletal muscle mass index. BIA: bioelectrical impedance analysis, which is used for the assessment of muscle mass. By the BIA method, a muscle mass of < 7.0 kg/m² in men and < 5.7 kg/m² in women indicates a reduction in muscle mass. HS: handgrip strength measurement. A handgrip strength of < 28 kg in men and < 18 kg in women is considered abnormal. GS: gait speed. 5R-ST5: the 5-repetition sit-to-stand test with a duration of > 30 s

< 28 kg for men and < 18 kg for women), gait speed (GS; < 1.0 m/s over 6 m), and the 5-repetition sit-to-stand (5R-ST5) test (> 30 s).

In parallel, laboratory analyses were performed to assess systemic biomarkers, including hemoglobin (Hb), albumin (ALB), and inflammatory markers (IL-4, IL-6, IL-8, TNF-α). Additionally, fecal 16 S rRNA sequencing was conducted to identify microbial taxa modulated by the interventions, aiming to elucidate potential microbiota-mediated mechanisms underlying sarcopenia improvement.

The ASMI (appendicular skeletal muscle mass index) of the FMT + RT group and the RT group was compared at the 4th week, 12th week, and 24th week after treatment. It was found that the ASMI of both groups improved compared with that before treatment. At the 4th week, the ASMI of the FMT + RT group showed improvement compared with that of the RT group, and the difference was statistically significant. By the 12th week, the FMT + RT group had a significant improvement compared with the RT group, and the difference was also statistically significant. At the 24th week, although the ASMI of the FMT + RT group decreased to some extent, it still showed improvement compared with that of the RT group, and the difference remained statistically significant (Fig. 2a).

During the observation of secondary indexes, we found that the SARC-F scores of both groups decreased at the 4th week, 12th week, and 24th week after treatment, and the decrease in the FMT + RT group was more significant than that in the RT group (Fig. 2b). There were significant differences in BIA (bioelectrical impedance analysis) and HS (handgrip strength) between the FMT + RT group and the RT group after treatment (Fig. 2c, d). There were differences in GS (gait speed) and 5R-ST5 (5-repetition sit-to-stand) between the FMT + RT group and the RT group

at the 4th week and 24th week after treatment, while no difference was observed at the 12th week (Fig. 2e, f).

After 4 weeks of treatment, the partial remission rate (PR) was 52.3% and the complete remission rate (CR) was 31.5% in the RT group. In comparison, the FMT + RT group had a PR of 64.2% and a CR of 45.3%. After 12 weeks, the PR in the RT group increased to 56.4%, while the CR decreased to 27.6%. In the FMT + RT group, the PR increased to 72.4% and the CR rose to 51.4%. The complete response rate at 24 weeks in the FMT + RT group was significantly higher than that in the RT group (47.1% vs. 32.2%, OR = 1.87, 95% CI: 1.21–3.42), suggesting that the combined intervention could substantially improve the therapeutic effect. At each follow-up time point, the treatment effect of the FMT + RT group was significantly better than that of the RT group (Table 4).

FMT enhances intestinal microbiota and nutritional indicators in sarcopenia patients

Microbiome analysis was conducted before and after treatment in thirty-three FMT + RT patients (Table S1). Compared to the pre-FMT group, the post-FMT group showed significantly higher levels of ALB, Hb, and SMI, while IL6 and TNF levels were markedly reduced (Fig. 3a). Significant correlations were observed among these indicators, including positive correlations of Hb with ALB, BMI, and SMI, and a negative correlation with IL6. Additionally, IL6 was negatively correlated with ALB but positively correlated with CD4. Positive correlations were also noted among TNF, CD4, and CD8. Moreover, a significant positive correlation was observed between SMI and BMI (Fig. S1a).

The study subsequently examined changes in patients' gut microbiota composition before and after FMT. Alpha diversity indices (Shannon, Simpson, PD) significantly increased in patients after receiving FMT treatment (Fig. 3b–d), though there was no significant difference in beta diversity between the two time points (Fig. S1b). A Venn diagram showed that both pre- and post-FMT groups shared 1,187 ASVs, while the pre-FMT and post-FMT groups contained 1,523 and 2,141 unique ASVs, respectively (Fig. S1c). Using LEfSe analysis to identify differentially changed microbes between pre- and post-FMT groups. Notably, *Veillonella* and *Erysipelatoclostridium* were characteristic enrichment in the pre-FMT group, while *Dorea*, *Roseburia*, *monoglobus*, *Barnesiella*, *colodextribacter*, *Blautia*, *Coproccoccus*, *Phascolarctobacterium*, *Collinsella*, *Agathobacter*, *Alistipes*, *Subdoligranulum*, and *Faecalibacterium* were prominent increasement in the post-FMT group (Fig. 4a). A microbial co-occurrence network constructed using SparCC revealed structural changes in the network pre- and post-FMT. In the pre-FMT group, *Faecalibacterium* served as the primary node with strong associations to other

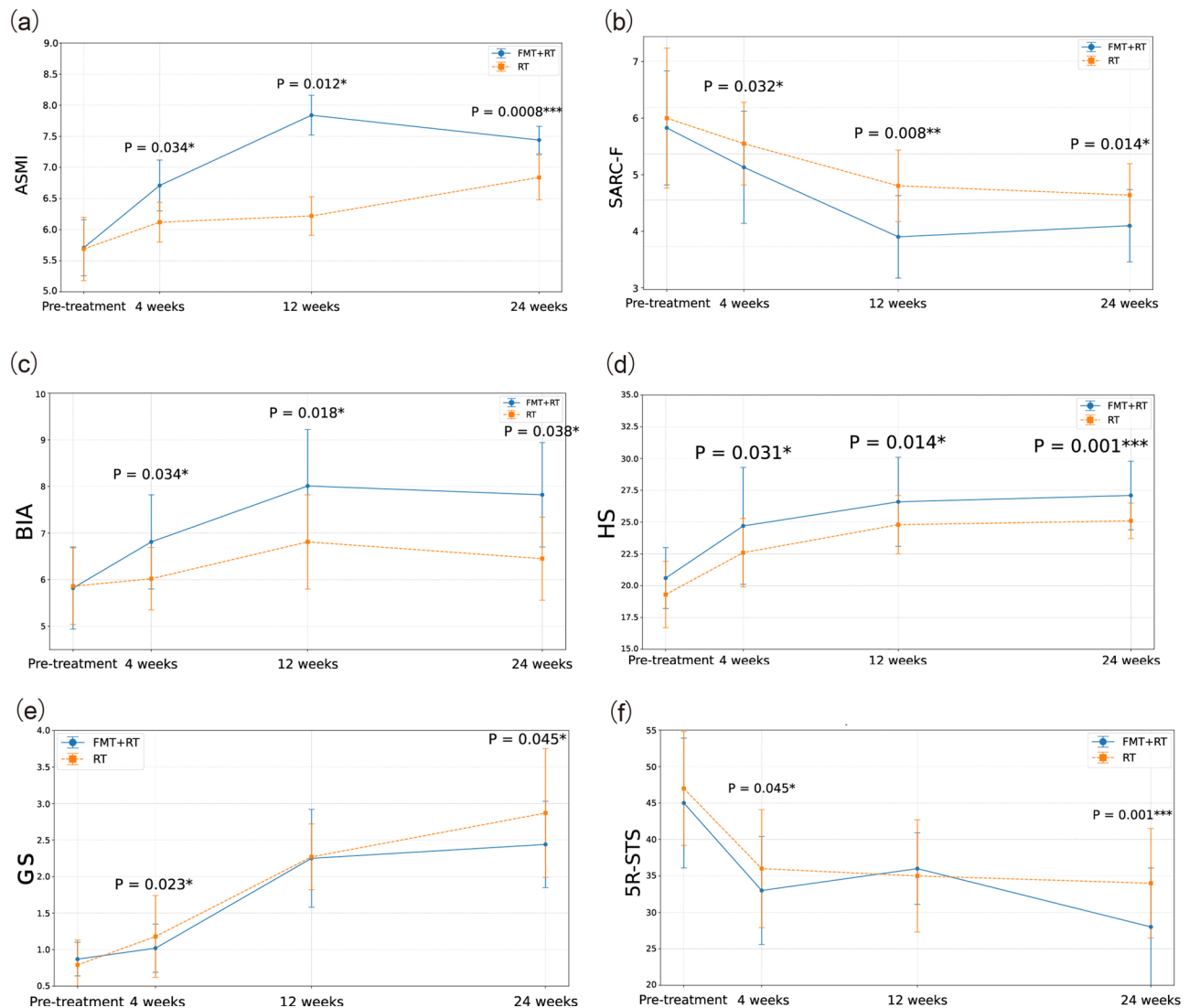


Fig. 2 Comparison of (A) appendicular skeletal muscle mass index (ASMI), (B) SARC-F, (C) BIA, (D) HS, (E) GS and (F) 5R-STs between the two groups before and after treatment. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 4 Follow-up results of partial response rate and complete response rate (with 95% confidence intervals and effect sizes)

	FMT + RT (N=85)	RT (N=87)	P value	FMT + RT % (95% CI)	RT % (95% CI)	Odds Ratio (95% CI)
Partial response						
Week 4	55/85 (64.7%)	45/87 (51.7%)	0.012	64.7% (54.1–74.2%)	51.7% (41.3–61.9%)	1.71 (1.12–3.02)*
Week 12	62/85 (72.9%)	49/87 (56.3%)	0.021	72.9% (63.1–81.5%)	56.3% (45.8–66.4%)	2.10 (1.25–3.89)*
Week 24	57/85 (67.1%)	48/87 (55.2%)	0.015	67.1% (56.5–76.5%)	55.2% (44.6–65.4%)	1.68 (1.10–2.98)*
Complete response						
Week 4	38/85 (44.7%)	27/87 (31.0%)	0.014	44.7% (34.2–55.6%)	31.0% (21.9–41.8%)	1.81 (1.14–3.14)*
Week 12	44/85 (51.8%)	24/87 (27.6%)	0.001	51.8% (41.1–62.3%)	27.6% (18.7–38.5%)	2.89 (1.72–5.24)*
Week 24	40/85 (47.1%)	28/87 (32.2%)	0.016	47.1% (36.5–57.9%)	32.2% (22.9–43.1%)	1.87 (1.21–3.42)*

Supplementary note: Calculation of confidence intervals: The 95% confidence interval (CI) for proportions (%) was calculated using the Wilson Score method, which is suitable for adjusting small sample sizes in binary data. The effect size was marked as Odds Ratio (OR) and its 95% CI, which was calculated by the Mantel-Haenszel method, reflecting the therapeutic advantage of the FMT+RT group over the RT group. The asterisk (*) indicates that the confidence interval does not include 1, which is statistically significant

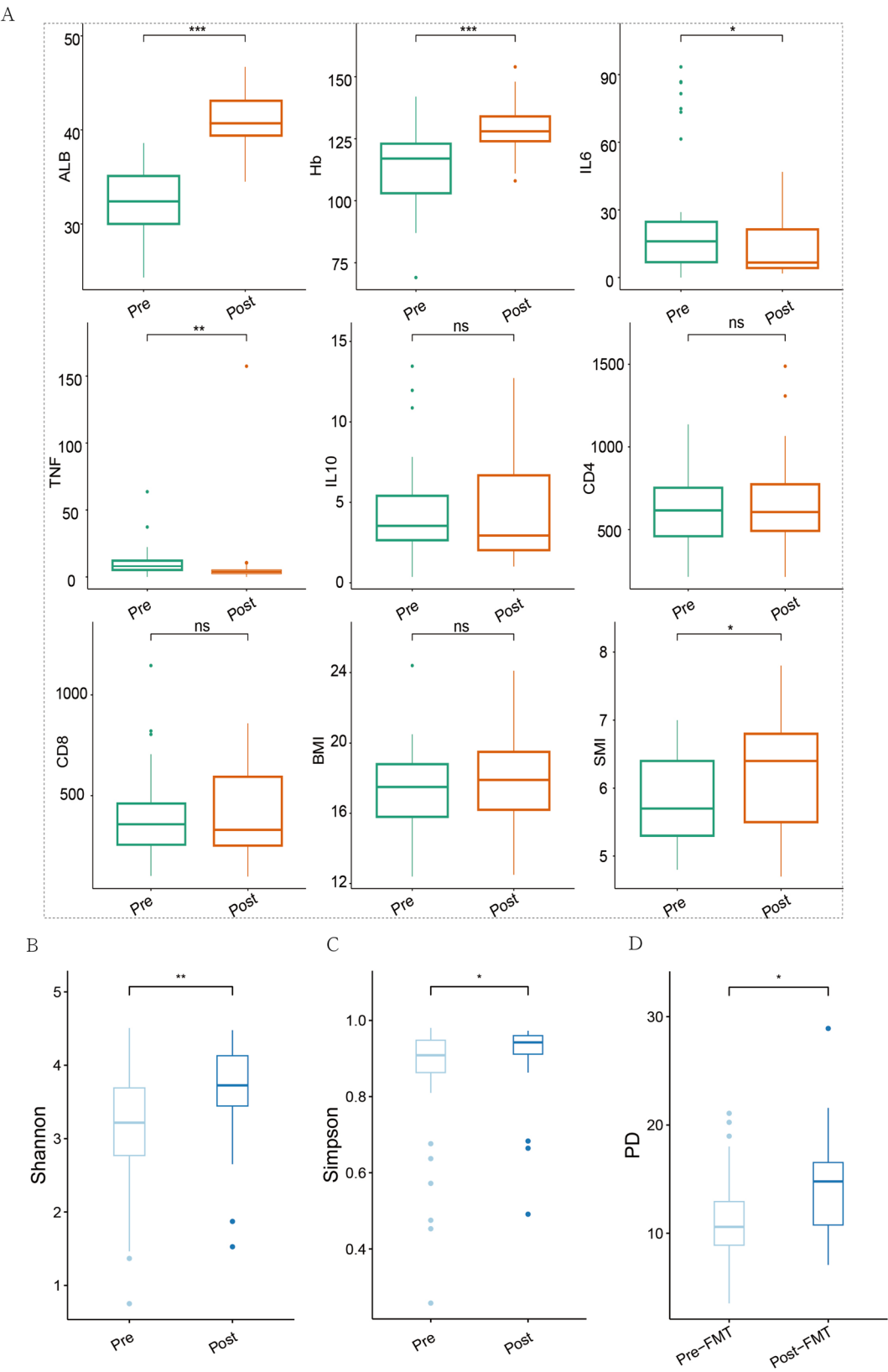


Fig. 3 (A) Clinical indications of patients before and after FMT. (B) Shannon index, (C) Simpson index, and (D) PD index before and after FMT

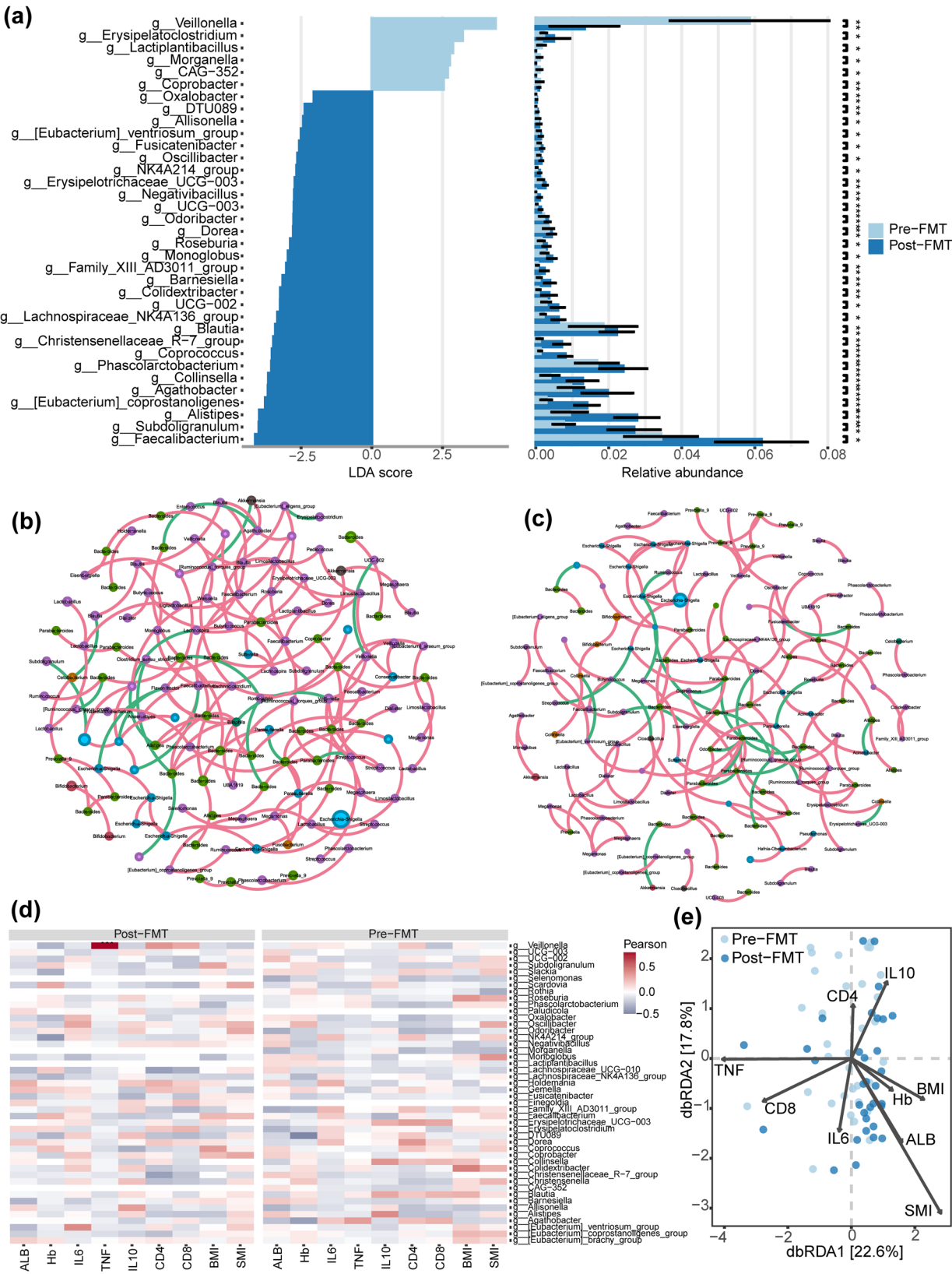


Fig. 4 (See legend on next page.)

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Fig. 4 (A) Differentially changed bacterial genera between patients before and after Fecal Microbiota Transplantation (FMT) were identified using Linear Discriminant Analysis (LDA) Effect Size (LEfSe) with LDA score threshold > 2.0 , highlighting taxa with significant abundance changes. Microbial co-occurrence networks, constructed using Sparse Correlations for Compositional Data (SparCC), illustrate the interactions and relationships among bacterial genera in the (B) pre-FMT group and (C) post-FMT group, revealing shifts in microbial community structure following FMT. (D) A Pearson correlation heatmap demonstrates the relationships between the abundance of bacterial genera and clinical indicators, providing insights into potential associations between gut microbiota composition and patient health outcomes. (E) Redundancy analysis (RDA) was performed to assess the contribution of clinical variables to the observed differences in the microbial community, highlighting key factors influencing microbiota composition before and after FMT. Together, these analyses provide a comprehensive view of the microbial changes induced by FMT and their potential links to clinical improvements

genera, while in the post-FMT group, *Parabacteroides* and *Bacteroides* emerged as central nodes with connections to other microbial genera (Fig. 4b-c).

In the correlations between microbiota and observed clinical indicators, a strong association was identified between *Veillonella* and TNF- α ($r=0.963$, $P<0.001$), which remained significant even after Benjamini-Hochberg correction (Fig. 4d). Additionally, several pre-correction significant correlations between specific microbiota and BMI or SMI attracted our attention. These included a notable positive correlation between *Colidextribacter* and BMI in the Pre-FMT group ($r=0.536$, unadjusted $P=0.001$), *Roseburia* and BMI ($r=0.458$, unadjusted $P=0.007$), *Monoglobus* and SMI ($r=0.451$, unadjusted $P=0.008$), and *Coprococcus* and BMI in the Post-FMT group ($r=0.426$, unadjusted $P=0.013$). Redundancy analysis (RDA) revealed that variables such as SMI, ALB, IL6, BMI, and Hb explained differences in the microbial community from similar angles. Similarly, CD4 and IL10, as well as CD8 and TNF- α , accounted for microbial community differences from comparable perspectives (Fig. 4e).

Microbial metabolic function improved in sarcopenia patients after receiving FMT treatment

Based on the PICRUSt2 EC analysis, the pre-FMT group displays enrichment in pathways supporting microbial resilience, notably through amino acid metabolism (*histidine kinase*) and cell wall synthesis (*serine-type D-Ala-D-Ala carboxypeptidase*). DNA stability mechanisms, such as *topoisomerase* and *DNA methyltransferase*, display adaptations suited to a less diverse, competitive environment, emphasizing structural integrity and survival over metabolic balance. In Post-FMT group, enriched pathways indicate improved energy and carbohydrate metabolism (*H(+)-transporting ATPase*, *citrate synthase*, *transketolase*), as well as enhanced nucleic acid synthesis (*adenosylcobalamin phosphatase*, *UMP/CMP kinase*). This shift reflects a healthier microbial balance, with functional pathways supporting metabolic stability and energy efficiency, likely contributing to gut homeostasis (Fig. 5a).

PICRUSt2 results was also annotated by Metacyc. In the pre-FMT group, there is a notable enrichment in pathways associated with cellular resilience and amino acid metabolism, such as glycogen biosynthesis and

L-isoleucine biosynthesis. Additional pathways, like adenine and adenosine salvage, indicate microbial reliance on nucleotide recycling, likely supporting survival in a dysbiotic gut environment. Post-FMT pathways indicate a shift toward enhanced metabolic balance and energy utilization, with enrichment in menaquinol biosynthesis and the pentose phosphate pathway. Increased activity in NAD biosynthesis and tRNA charging suggests improved cellular processes, reflecting a microbiome favoring efficient metabolism and functional stability post-FMT (Fig. 5b).

Discussion

Among the existing intervention methods, exercise intervention has clear effect but poor compliance, nutritional supplement-based support but insufficient effect alone, and probiotic therapy mechanism is novel but also inadequate [5, 22]. The changes in the composition and function of the intestinal microbiome community in age-related sarcopenia population are very consistent with the technical principle of microbiome transplantation. Current evidence highlights the multi-target potential of FMT in sarcopenia, including restoring gut barrier integrity, modulating systemic inflammation, and enhancing muscle anabolism via microbial metabolites [12, 23]. Preliminary studies suggest FMT may offer synergistic benefits by addressing gut dysbiosis-driven pathologies, whereas dietary or pharmacological interventions primarily target isolated pathways.

In this study, FMT + RT therapy demonstrated a superior treatment response compared to RT alone. This finding implies substantial potential for ameliorating sarcopenia through gut microbiota regulation. The improvement of clinical markers in post-treatment group, such as the elevation of ALB, Hb, and SMI and the reduction of IL6 and TNF levels, indicates that FMT might influence sarcopenia development at multiple physiological levels. FMT may improve sarcopenia through the modulation of the gut microbiota via several potential mechanisms. The gut microbiota influences muscle metabolism and inflammatory responses through metabolites such as short-chain fatty acids (SCFAs). Serving as the primary energy source for intestinal epithelial cells, butyrate in particular enhances the expression of tight junction proteins (such as occludin and claudin-1) by activating the AMPK/mTOR signaling pathway, thereby reducing

intestinal permeability while simultaneously stimulating goblet cells to secrete mucin MUC2, thereby strengthening the mucosal barrier [24]. Furthermore, SCFAs promote intestinal epithelial repair through inhibition of histone deacetylase (HDAC) and modulate immune cell function (including expansion of Treg cells and M2 macrophages) to maintain barrier integrity [25]. From an anti-inflammatory perspective, SCFAs mitigate intestinal inflammation by blocking the NF- κ B pathway and NLRP3 inflammasome activation, which reduces the release of pro-inflammatory cytokines (TNF- α , IL-6) while elevating anti-inflammatory mediators (IL-10), this anti-inflammatory effect consequently reduces muscle catabolism and promotes muscle mass accretion [26]. Additionally, the gut microbiota plays a role in regulating insulin sensitivity and energy metabolism, affecting the balance between muscle protein synthesis and degradation. FMT may also indirectly impact muscle health by modulating bile acid metabolism and vitamin synthesis [27, 28]. For instance, bile acids can activate the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor (TGR5), thereby regulating muscle metabolism and inflammation. The synthesis of vitamins D and K, which are crucial for muscle function and bone health, also depends on the gut microbiota. Therefore, FMT may improve muscle mass and function in patients with sarcopenia by regulating the gut microbiota through multiple pathways.

Microbial by-products, such as LPS, can not only induce chronic inflammation but also contribute to insulin resistance. This reduces the ability of muscle cells to utilize glucose, causing them to rely on glycogen or fat, ultimately leading to muscle mass and functional loss [29, 30]. Furthermore, SCFAs produced by intestinal microbial metabolism play a crucial role in intestinal energy metabolism, anti-inflammation, protection of the intestinal barrier, and regulation of intestinal motility. These effects are mainly mediated through the inhibition of histone deacetylases (HDACs) or activation of SCFA receptors. SCFAs can exert their effects by inhibiting HDACs and activating histone acetyltransferases, with butyrate being the most important HDAC inhibitor [26]. Therefore, a reduction in SCFA production due to microbial dysbiosis adversely impacts intestinal homeostasis and inflammation. FMT treatment significantly increases the abundance of SCFA-producing bacteria, such as *Faecalibacterium*, *Roseburia*, and *Dorea*, which helps improve intestinal homeostasis, mucosal repair, nutrient absorption, and muscle growth. This could be one of the reasons why the FMT + RT group in this study showed the best treatment results.

We found that before FMT treatment, the abundance of *Erysipelatoclostridium* in the patient's feces was relatively high. *Erysipelatoclostridium* is associated with

immune regulation and inflammation, and its increased abundance may exacerbate systemic inflammation and intestinal barrier dysfunction, indirectly promoting muscle breakdown and functional decline. After FMT, the abundance of bacterial genera such as *Dorea*, *Roseburia*, and *Faecalibacterium* increased, potentially promoting muscle health through multiple mechanisms and offering potential benefits for the treatment of sarcopenia. These genera can ferment dietary fiber to produce SCFAs, such as butyrate, propionate, and acetate, which provide energy for muscles, promote protein synthesis, and reduce muscle breakdown [31, 32]. Additionally, they exhibit anti-inflammatory effects by inhibiting the release of pro-inflammatory factors (e.g., IL-6, TNF- α), thereby alleviating chronic inflammation-induced muscle damage. These genera also enhance intestinal barrier function, reducing the entry of endotoxins into the bloodstream and subsequently lowering systemic inflammation and oxidative stress. *Roseburia*, as one of the primary producers of butyrate, strengthens the intestinal barrier and reduces the entry of endotoxins (e.g., LPS) into the bloodstream, thereby decreasing systemic inflammation [33]. Through its anti-inflammatory effects and improvement of gut health, *Roseburia* may indirectly protect muscles from inflammation-mediated breakdown.

Although this study is retrospective and may have some inherent biases, we have made every effort during the study design phase to minimize their impact. The patient groups (FMT + RT vs. RT) were not randomized, potentially introducing differences due to clinical characteristics or doctor preferences. While Table 3 shows no significant differences in baseline indicators (e.g., age, BMI, SARC-F score), further verification is needed to account for all potential confounders (e.g., nutritional status, comorbidities). Known confounders (e.g., age, gender, inflammatory markers) were included in statistical analysis to minimize inter-group differences. Retrospective data may miss key indicators (e.g., patient compliance, dietary details), and measurement methods (e.g., BIA, TNF- α detection) may have inconsistencies. Microbiome analysis could be affected by variations in sample collection, storage, or sequencing. To address this, we supplemented data through medical record reviews and surveys (e.g., nutritional intake) and ensured consistency via cross-validation. Unmeasured confounders (e.g., socioeconomic status, psychological state) may influence outcomes and will be acknowledged in the discussion, with suggestions for future studies to include more comprehensive variables.

Despite the achievements in this study, certain limitations remain. Firstly, this is a single-center study with a relatively small sample size, which may introduce selection bias and potentially affect the generalizability of the

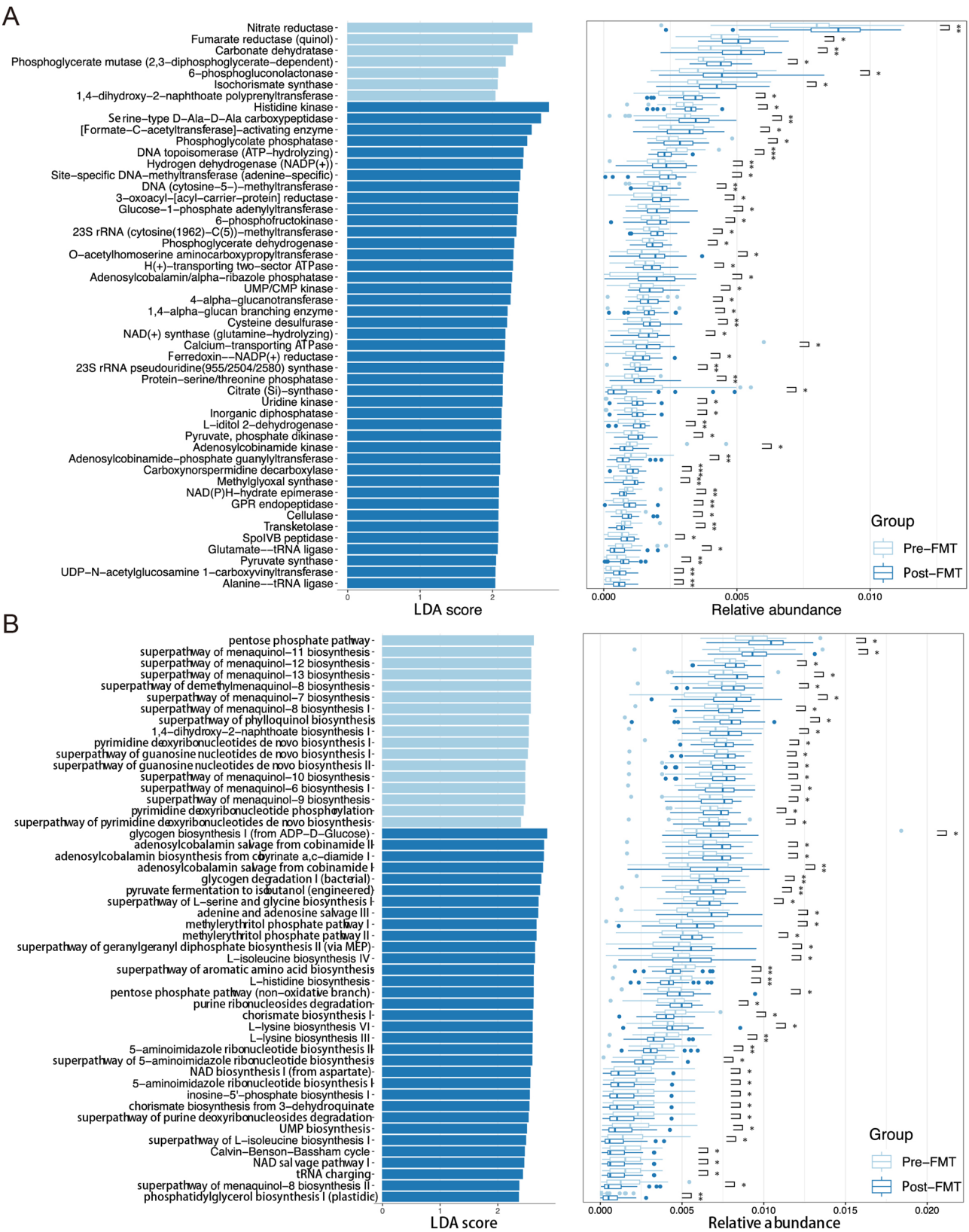


Fig. 5 (See legend on next page.)

(See figure on previous page.)

Fig. 5 Differential functional pathways between the Pre-FMT (light blue) and Post-FMT (blue) groups, annotated using **(A)** Enzyme Commission (EC) numbers and **(B)** MetaCyc pathway database. The Linear Discriminant Analysis (LDA) scores, indicating the effect size of differentially abundant pathways, are shown on the left side of the figure. The relative abundances of these pathways, reflecting their proportional representation in the microbial community, are displayed on the right side. This analysis highlights significant shifts in microbial metabolic functions following FMT, providing insights into the potential mechanisms underlying its therapeutic effects

results. Future multi-center, large-sample studies are thus required to further verify our findings. Secondly, although changes in intestinal microbiota and clinical indicators after FMT have been observed, long-term follow-up and observation are necessary to assess the long-term effects of microbiota transplantation and potential adverse reactions. Additionally, this study primarily relies on bioinformatics analysis. While this approach enables a comprehensive understanding of intestinal microbiota changes, further experimental investigations are needed to elucidate the molecular mechanisms between the microbiota and the host. Such investigations could involve in-depth exploration of specific signaling pathways and molecular targets through which the microbiota affects muscle metabolism using animal models and cell experiments. Finally, during the FMT process, the selection criteria for donor microbiota and the transplantation protocol can be further optimized to enhance the therapeutic effect and minimize the impact of individual differences.

Conclusions

In this single-center study, bioinformatics analysis was used to assess microbiota transplantation for sarcopenia treatment. Results showed FMT effectively improved patient symptoms, with high response rates and significant clinical improvements. FMT also altered gut microbiota diversity, composition, biomarkers, and metabolic function, closely linked to clinical outcomes. This study supports microbiota transplantation for sarcopenia and highlights the gut microbiota's role in its progression and treatment. However, larger multi-center studies and deeper mechanistic research are needed to refine knowledge and develop better treatment strategies.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12967-025-06557-5>.

Supplementary Table S1

Supplementary Figure S2

Author contributions

Bo Yang designed the whole project and wrote the main manuscript text, and Xinhui Li provided the design ideas, Jiahui Wang provided the sample information, and Yue Xu analyzed the microbiota data, and Le Wang and Zhifeng Wu collected information and samples from patients, and Di Zhao and Long Huang were in charge of monitoring the treatment effectiveness in patients, and Ning Li, Qiyi Chen and Zhongchen Liu supervised and revised the entire study.

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Data availability

The detail baseline information of our cohort is available in the **Supplementary information**.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Shanghai Tenth People's Hospital. All patients provided written informed consent for this study. All methods in this study carried out in accordance with the **Declaration of Helsinki**. Permission to use the patient's samples was obtained from the Ethics Committee of the Shanghai Tenth People's Hospital.

Consent for publication

Not applicable.

Competing interests

Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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