Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Feasibility of Home-Based Exercise in Primary Biliary Cholangitis: A Prospective Five-Patient Pilot Study with Body Composition, Quality-of-Life and Gut Microbiota Assessments

Saori Endo
Niigata University
Hiroteru Kamimura
hiroteruk@med.niigata-u.ac.jp
Niigata University
Suguru Miida
Niigata University
Hiroki Natsui
Niigata University
Hiroki Maruyama
Niigata University
Shunta Yakubo
Niigata University
Masaru Kumagai
Niigata University
Tomoaki Yoshida
Niigata University
Naruhiro Kimura
Niigata University
Kentaro Tominaga
Niigata University
Hiroyuki Abe
Niigata University
Tadashi Ariyoshi
Miyarisan Pharmaceutical Co., Ltd
Kentaro Oka
Miyarisan Pharmaceutical Co., Ltd
Motomichi Takahashi
Miyarisan Pharmaceutical Co., Ltd

Yuichiro Hosoi
Keio University School of Medicine
Michiyuki Kawakami
Keio University School of Medicine
Kenya Kamimura
Niigata University
Tetsuya Tsuji
Keio University School of Medicine
Shuji Terai
Niigata University

Research Article

Keywords: primary biliary cholangitis, pilot study, feasibility, exercise therapy, rehabilitation, supportive care, body composition, gut microbiota, 16S rRNA sequencing

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10084232/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: Competing interest reported. Tadashi Ariyoshi, Kentaro Oka and Motomichi Takahashi are employees of Miyarisan Pharmaceutical Co., Ltd. Kenya Kamimura serves as Guest Editor for the Special Issue “Nutritional Support for Improving the Life Quality in Liver Disease”; if the manuscript is considered for that Special Issue, he will not participate in editorial handling or decision-making. The other authors declare no conflict of interest. Employees of Miyarisan Pharmaceutical Co., Ltd. contributed to microbiota-related analysis and interpretation as described in the author contribution statement. The funding agency had no role in the design, execution, interpretation, writing of the study or decision to submit the manuscript for publication.

Feasibility of Home-Based Exercise in Primary Biliary Cholangitis: A Prospective Five-Patient Pilot Study with Body Composition, Quality-of-Life and Gut Microbiota Assessments

Article type: Research

Authors: Saori Endo[1], Hiroteru Kamimura[1]*, Suguru Miida[1], Hiroki Natsui[1], Hiroki Maruyama[1], Shunta Yakubo[1], Masaru Kumagai[1], Tomoaki Yoshida[1], Naruhiro Kimura[1], Kentaro Tominaga[1], Hiroyuki Abe[1], Tadashi Ariyoshi[2], Kentaro Oka[2], Motomichi Takahashi[2], Yuichiro Hosoi[3], Michiyuki Kawakami[3], Kenya Kamimura[4], Tetsuya Tsuji[3] and Shuji Terai[1]

Affiliations:

1 Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan

2 R&D Division, Miyarisan Pharmaceutical Co., Ltd., Saitama, Japan

3 Department of Rehabilitation Medicine, Keio University School of Medicine, Tokyo, Japan

4 Department of General Medicine, School of Medicine, Niigata University, Niigata, Japan

* Correspondence: Hiroteru Kamimura, MD, PhD; E-mail: hiroteruk@med.niigata-u.ac.jp; Tel.: +81-25-227-2207; Fax: +81-25-227-0776; ORCID: 0000-0002-9135-3092

Trial registration: UMIN Clinical Trials Registry, UMIN000051577. Registered 1 August 2023.

Abstract

Background: Evidence on exercise therapy in primary biliary cholangitis (PBC) remains limited, particularly regarding feasibility, body composition, quality of life, and the gut-liver axis. This prospective pilot study evaluated a 12-week home-based exercise program in outpatients with PBC.

Methods: The target sample size was five enrolled participants, chosen pragmatically to test recruitment, intervention delivery, adherence monitoring, serial clinical assessments and stool sampling rather than to test efficacy. Five female outpatients with PBC, including three with PBC alone and two with PBC/autoimmune hepatitis overlap, completed a home-based program combining walking and lower-limb resistance exercise. Primary feasibility outcomes were recruitment yield, completion of the intervention, attendance at the scheduled 3-month assessment, adherence to walking and resistance exercise, and exercise-related adverse events. Progression benchmarks for a future controlled study included recruitment of the planned sample, at least 80% completion, at least 80% follow-up attendance, acceptable safety, and interpretable adherence data.

Results: The recruitment target was reached: five of 35 assessed patients were enrolled (14.3%; exact 95% confidence interval [CI] 4.8-30.3%). All five participants completed the intervention and the 3-month assessment (100%; 95% CI 47.8-100%). No exercise-related adverse events occurred (0%; 95% CI 0-52.2%). Mean achievement of individualized step targets was 45%, below the desired adherence benchmark, whereas mean resistance-exercise adherence was 74%. Body weight was generally maintained, skeletal muscle index increased slightly in three patients, and 6-minute walk distance increased in four patients. Total bilirubin decreased descriptively over repeated measurements. Microbiota analyses showed no consistent pre-post separation in alpha diversity, beta diversity, genus-level composition or PICRUSt2-predicted pathways. Some descriptive genus-level shifts involved taxa that include butyrate-producing members, but fecal short-chain fatty acids were not measured.

Conclusions: The planned pilot sample was recruited, and progression benchmarks were met for intervention completion, follow-up attendance and safety in this 5-patient PBC pilot study.

Walking adherence was below the desired benchmark and should be addressed before a larger controlled study. Clinical and microbiota results should be regarded as exploratory and hypothesis-generating.

Trial registration: UMIN Clinical Trials Registry, UMIN000051577. Registered 1 August 2023.

Keywords: primary biliary cholangitis; pilot study; feasibility; exercise therapy; rehabilitation; supportive care; body composition; gut microbiota; 16S rRNA sequencing

Key messages regarding feasibility

- What uncertainties existed regarding feasibility? It was uncertain whether stable outpatients with PBC could complete a 12-week home-based program combining walking, lower-limb resistance exercise, serial clinical assessments and stool microbiota sampling without exercise-related adverse events.
- What are the key feasibility findings? Recruitment from 35 assessed patients yielded five enrolled participants; all five completed the program and 3-month assessment, no exercise-related adverse events occurred, resistance-exercise adherence was relatively high, and walking-target achievement was variable.
- What are the implications for the design of the main study? A larger controlled study could proceed after refining recruitment procedures, symptom-adjusted walking targets, adherence support, PBC-specific quality-of-life measurement, and direct metabolic profiling of bile acids and short-chain fatty acids. Walking adherence is the main protocol component requiring revision.

Background

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease characterized by immune-mediated injury of small intrahepatic bile ducts. It predominantly affects middle-aged and older women and can progress from asymptomatic cholestasis to fibrosis, cirrhosis, portal hypertension and hepatic failure. Even when hepatic reserve is preserved, fatigue, pruritus, sleep disturbance, anxiety, depressed mood and reduced physical activity can impair health-related quality of life; therefore, management should address symptoms and physical function in addition to biochemical response and long-term prognosis [1].

The gut-liver axis has become an important framework for understanding PBC. Altered gut microbial profiles have been reported in patients with PBC, and partial restoration after ursodeoxycholic acid (UDCA) treatment has been described [2]. Other studies have linked microbiota and microbial metabolites to the response to bile acid sequestrants, treatment response and experimental PBC-like phenotypes [3-6]. These findings suggest that microbiota-related pathways may be relevant to cholestatic autoimmune liver disease, although causality in humans remains uncertain.

Exercise and diet intervention has been shown to modify microbiome networks in patients with nonalcoholic fatty liver disease [7]. Exercise therapy is also increasingly recognized as a non-pharmacological strategy for chronic liver disease, as reflected in recent liver rehabilitation guidance [8]. Physical activity may influence intestinal motility, gut barrier function, bile acid metabolism, microbial metabolites and systemic inflammation through the hepatobiliary-gut axis [9]. Exercise may rebalance enterohepatic bile acid profiles in nonalcoholic fatty liver disease [10], and exercise has been reported to alter gut microbiota composition and function in lean and obese humans [11].

In PBC, the EXCITED clinical trial showed that a home-based aerobic and resistance exercise program may attenuate fatigue, supporting the feasibility of home-based exercise in this population [12]. However, few studies have evaluated exercise intervention together with serial clinical assessments and gut microbiota analysis in patients with PBC. We therefore conducted an exploratory prospective pre-post pilot study in five patients with PBC. The primary aim was to evaluate the feasibility and safety of a 12-week home-based exercise program. Secondary and exploratory aims were to describe changes in body composition, physical function, liver-related laboratory parameters, disease-related quality of life and gut microbiota profiles. Given the small sample size and absence of a control group, this study was designed to generate feasibility data rather than establish efficacy.

Methods

Study design, setting and feasibility objectives

This prospective, single-center, non-randomized pre-post pilot study was conducted at Niigata University Medical and Dental Hospital. Reporting was informed by the journal guidance for non-randomized pilot and feasibility studies and by the CONSORT extension for pilot and feasibility trials where applicable [23,24]. Thirty-five female outpatients with PBC were assessed for eligibility, and five patients who met the study criteria and provided written informed consent were enrolled (Fig. 1).

The primary feasibility outcomes were recruitment yield among assessed patients, completion of the 12-week intervention, attendance at the scheduled 3-month assessment, adherence to prescribed aerobic and resistance exercise, and exercise-related adverse events. These feasibility outcomes were selected to determine whether a future controlled study would be practical in

stable outpatients with PBC and whether protocol components required refinement before progression.

Sample size rationale and progression criteria

The target sample size was five enrolled participants. This pragmatic target was chosen because PBC is uncommon, the intervention required repeated outpatient assessments and stool sampling, and the primary purpose was to test feasibility procedures rather than to estimate efficacy. The sample size was therefore not based on statistical power. Instead, the planned sample was intended to determine whether recruitment, home-based exercise delivery, adherence monitoring, serial clinical assessments and stool collection could be completed and to generate feasibility estimates for a future controlled study.

Progression to a future controlled study was judged using pragmatic feasibility benchmarks rather than efficacy thresholds: recruitment of the planned five participants from the assessed clinic population, with an approximate recruitment yield of at least 10%; completion of the 12-week intervention by at least 80% of enrolled participants; attendance at the scheduled 3-month assessment by at least 80%; no exercise-related serious adverse events and no exercise-related adverse events requiring discontinuation; and interpretable adherence data. For adherence, mean resistance-exercise adherence of at least 70% was considered acceptable, whereas mean step-target achievement below 70% was interpreted as indicating that walking goals and adherence support should be revised before a larger study.

Participants

PBC was diagnosed according to Japanese PBC clinical practice guidelines and internationally accepted diagnostic concepts based on cholestatic hepatobiliary enzyme elevation, antimitochondrial antibody status, histological findings and clinical course [13].

PBC/autoimmune hepatitis (AIH) overlap was assessed with reference to the Paris criteria, considering cholestatic features, hepatocellular injury, autoantibodies, immunoglobulin G, histology and treatment course [14]. Three patients had PBC alone and two were judged to have PBC/AIH overlap.

Patients were excluded if they had recent antibiotic use, new initiation or modification of probiotics or prebiotics, active infection, inflammatory bowel disease, difficulty providing stool samples, or a condition judged by the attending physician to make exercise intervention unsuitable. Background UDCA was continued in all patients, and low-dose prednisolone was continued in the two patients with PBC/AIH overlap. Diet, bowel habits, proton pump inhibitor use, supplements and other potential microbiota-related confounders were not standardized.

Exercise intervention

The intervention consisted of a 12-week home-based program combining aerobic walking and resistance exercise focused on lower-limb muscles. Resistance exercises targeted the iliopsoas, quadriceps, gluteus medius and triceps surae using body weight or elastic bands. Patients were instructed to perform three sets of 10 repetitions for each exercise at least 3 days per week. Aerobic exercise was based on walking, with a target perceived intensity of 11-13 on the Borg scale.

Individual daily step targets were set by adding 1000 steps to the pre-intervention average, with a lower limit of 3000 steps/day and an upper limit of 8000 steps/day. Exercise performance was monitored using outpatient instruction, exercise diaries and activity meter records. Adherence was reviewed at 1 and 2 months, and patients were encouraged to continue exercise when needed. Exercise-related adverse events, including falls, musculoskeletal symptoms requiring discontinuation, hospitalization and worsening liver-related complications, were assessed by outpatient interviews and diary review.

Clinical assessments

Body composition was assessed using body weight, body mass index, skeletal muscle index (SMI), body fat percentage, and limb and trunk muscle mass. SMI was calculated using body composition measurements obtained with multi-frequency bioelectrical impedance analysis (InBody S10; InBody Japan, Tokyo, Japan). Physical function was assessed using handgrip strength and 6-minute walk distance. Liver stiffness and controlled attenuation parameter were measured as supportive assessments of fibrosis and steatosis.

Health-related quality of life was evaluated using the Chronic Liver Disease Questionnaire (CLDQ) before and after the intervention. Laboratory measurements included total and direct bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (gamma-GTP), cholinesterase, ammonia, metabolic markers, complete blood count, coagulation indices, immunoglobulins, hyaluronic acid, bile acids, type IV collagen 7S and Mac-2 binding protein glycosylation isomer. ALP activity was measured using an IFCC-traceable method.

Gut microbiota analysis

Stool samples were collected before the intervention and at 3 months, then stored frozen until analysis. DNA extraction was performed according to the method of Takahashi et al.; after pretreatment and crude extraction, purification was performed using PI-480 (Kurabo Industries, Osaka, Japan) [15]. The V3-V4 region of the bacterial and archaeal 16S rRNA gene was amplified using universal primers (341F/805R), and paired-end sequencing was performed on the MiSeq platform (Illumina, San Diego, CA, USA) [15,16].

Sequence data were processed using QIIME 2 version 2021.2, and denoising and amplicon sequence variant inference were performed using DADA2 [17,18]. Taxonomic annotation was based on the SILVA database, and predicted functional profiling was performed using

PICRUSt2 [19,20]. Alpha diversity was assessed using Chao1 richness and Shannon diversity, and beta diversity was evaluated using weighted UniFrac distances. Because 16S rRNA sequencing has limited resolution at the species and strain levels, microbiota results were interpreted primarily at the genus level.

Statistical analysis

Continuous variables are presented as medians [interquartile ranges] or individual values, as appropriate. No formal hypothesis testing was conducted in the revised analyses, and p values are not reported. Baseline-to-3-month changes and repeated measurements are summarized descriptively using medians, interquartile ranges and individual trajectories. Genus-level relative abundance and PICRUSt2-predicted pathway analyses were considered exploratory and are summarized using descriptive differences and directions of change.

Exact binomial 95% confidence intervals were calculated for recruitment yield, completion, follow-up attendance and exercise-related adverse events. Because the sample size was only five patients and the study had no control group, clinical and microbiota findings were not interpreted as evidence of efficacy or causality.

Results

Baseline characteristics

Baseline characteristics are summarized in Table 1. All five patients were female, and the median age was 68 years. Three patients had PBC alone and two had PBC/AIH overlap. All patients had a Child-Pugh score of 5, indicating preserved hepatic reserve. UDCA was continued in all patients, and low-dose prednisolone was continued in the two patients with PBC/AIH overlap. Median baseline body weight was 55.7 kg, median SMI was 5.9 kg/m2, median 6-minute walk distance was 481.0 m and median total bilirubin was 0.8 mg/dL.

Table 1. Baseline characteristics of the five patients.

Characteristic	Pt1	Pt2	Pt3	Pt4	Pt5
Age, years	68	62	73	57	68
Sex	Female	Female	Female	Female	Female
Diagnosis	PBC	PBC/AIH overlap	PBC	PBC/AIH overlap	PBC
UDCA	Yes, 400 mg	Yes, 600 mg	Yes, 300 mg	Yes, 300 mg	Yes, 600 mg
Prednisolone	No	Yes, 5 mg	No	Yes, 5 mg	No
Child-Pugh score	5	5	5	5	5
Body weight, kg	52.8	55.7	50.7	57.6	69.4
BMI, kg/m2	23.2	21.8	20.1	24.6	26.1
SMI, kg/m2	4.7	5.9	5.7	6.3	6.6
6-minute walk distance, m	354.4	456.5	481.0	498.2	501.0
Total bilirubin, mg/dL	0.4	0.9	0.8	0.8	0.8
Albumin, g/dL	4.0	3.9	4.2	4.9	4.2
ALP, U/L	46	43	49	38	86
gamma-GTP, U/L	35	11	21	15	45
CLDQ total score	145	141	184	157	167

AIH autoimmune hepatitis, ALP alkaline phosphatase, BMI body mass index, CLDQ Chronic Liver Disease Questionnaire, gamma-GTP gamma-glutamyl transpeptidase, PBC primary biliary cholangitis, SMI skeletal muscle index, UDCA ursodeoxycholic acid. Background UDCA and low-dose prednisolone for PBC/AIH overlap were continued throughout the study.

Feasibility, adherence and safety

Five of 35 assessed patients were enrolled, giving a recruitment yield of 14.3% (exact 95% CI 4.8-30.3%) and achieving the planned pilot sample size of five participants. All five patients completed the 12-week intervention and the scheduled 3-month assessment, resulting in a completion and follow-up attendance rate of 100% (5/5; exact 95% CI 47.8-100%) (Fig. 1; Table 2). No exercise-related adverse events, falls, musculoskeletal symptoms requiring discontinuation, hospitalization or worsening liver-related complications occurred during the intervention period (0/5; exact 95% CI 0-52.2%).

Daily step targets were individualized within the range of 3000-8000 steps/day. Mean step-target achievement varied among patients, with an overall mean of 45%, which was below the desired benchmark of 70% and indicates that walking goals and adherence support require refinement before a larger study. Resistance exercise adherence was relatively high, with an overall mean of 74%, meeting the desired benchmark. Pt3 maintained high achievement for both walking and resistance exercise, whereas Pt2 showed lower adherence to both components. These findings suggest that a home-based program can be implemented in this selected population, but the walking component requires protocol revision.

Table 2. Feasibility outcomes, adherence and safety during the 12-week intervention.

Outcome	Progression target/benchmark	Observed result	Interpretation
Target sample size/recruitment yield	Enroll planned pilot sample (n = 5); approximate recruitment yield >=10%	5/35, 14.3% (exact 95% CI 4.8-30.3%)	Met; planned sample recruited
Completion	>=80% reach the end of the 12-week intervention	5/5, 100% (exact 95% CI 47.8-100%)	Met
3-month assessment attendance	>=80% attend scheduled assessment after intervention	5/5, 100% (exact 95% CI 47.8-100%)	Met

Outcome	Progression target/benchmark	Observed result	Interpretation
Exercise-related adverse events	No serious exercise-related adverse events and no event requiring discontinuation	0/5, 0% (exact 95% CI 0-52.2%)	Met; precision limited by n = 5
Mean step-target achievement	>=70% desirable; <70% indicates need to refine walking goals/support	45% overall; individual means 6-92%	Not met; revise walking component
Mean resistance-exercise adherence	>=70% desirable	74% overall; individual means 36-100%	Met, but individual variability remains

Clinical changes

During the 12-week intervention, body weight was generally maintained (Table 3). Median body weight was 55.7 kg at baseline and 56.6 kg at 3 months. Median SMI was 5.9 kg/m2 at baseline and 5.9 kg/m2 at 3 months; in individual baseline-to-3-month comparisons, SMI increased slightly in three patients, was unchanged in one and decreased in one.

Six-minute walk distance increased in four of five patients, with a median change of +35.6 m [11.8 to 44.5]. The CLDQ total score increased in three of four evaluable patients, with a median change of +8 points [3 to 11]. These changes are reported descriptively and should not be interpreted as evidence of efficacy.

Total bilirubin decreased across repeated measurements, with median values of 0.8 mg/dL at baseline, 0.7 mg/dL at 1 month, 0.7 mg/dL at 2 months and 0.6 mg/dL at 3 months. In individual baseline-to-3-month comparisons, total bilirubin decreased in all five patients, with a median change of -0.2 mg/dL [-0.2 to -0.1]. Because baseline bilirubin values were low, the absolute change was small and no control group was included, this finding was interpreted descriptively. Albumin, AST, ALT, ALP and gamma-GTP did not show consistent directional changes.

Table 3. Group summary of selected clinical variables during the 12-week intervention.

Variable	0 month	1 month	2 months	3 months
Body weight, kg	55.7 [52.8-57.6]	56.8 [52.7-59.0]	56.9 [52.1-59.2]	56.6 [52.0-59.3]
SMI, kg/m2	5.9 [5.7-6.3]	5.9 [5.9-6.5]	5.9 [5.7-6.5]	5.9 [5.9-6.4]
Total bilirubin, mg/dL	0.8 [0.8-0.8]	0.7 [0.7-0.8]	0.7 [0.6-0.8]	0.6 [0.6-0.6]
Albumin, g/dL	4.2 [4.0-4.2]	4.1 [4.1-4.5]	4.3 [4.3-4.4]	4.0 [3.9-4.1]
AST, U/L	20 [20-29]	19 [18-29]	19 [18-32]	20 [17-26]
ALT, U/L	15 [13-18]	13 [13-19]	15 [11-17]	13 [11-16]
ALP, U/L	46 [43-49]	48 [46-73]	47 [47-56]	57 [46-62]
gamma-GTP, U/L	21 [15-35]	22 [14-42]	16 [15-37]	19 [15-37]

Values are median [interquartile range]. All clinical variables are summarized descriptively without p values. ALP alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, gamma-GTP gamma-glutamyl transpeptidase, SMI skeletal muscle index.

Gut microbiota findings

Alpha diversity, assessed using Chao1 richness and Shannon diversity, did not show a consistent pre-post pattern (Fig. 2). Weighted UniFrac analysis did not show clear pre-post separation in beta diversity (Fig. 3). Individual samples shifted to some extent, but inter-individual differences were larger than any consistent intervention-related shift.

Genus-level microbiota composition for all five patients is shown in Fig. 4. Exploratory genus-level analysis was summarized by mean and median relative-abundance differences rather than p values (Table 4). In descriptive analysis, Dorea, Agathobacter, Acidaminococcus and Faecalibacterium were relatively higher before the intervention, whereas Clostridium sensu stricto 1 and Roseburia were relatively higher after the intervention. PICRUSt2 analysis was also treated as descriptive pathway-level exploration (Fig. 5). These findings were treated as hypothesis-generating only.

Several genera showing numerical pre-post differences included taxa with recognized short-chain fatty-acid-producing capacity. In particular, Roseburia and Faecalibacterium are commonly regarded as butyrate-producing genera in the human gut [25-27]. The relative increase in Roseburia after the intervention may therefore be compatible with a potential butyrate-related microbial shift. However, this interpretation was not consistent across all butyrate-producing taxa, because Faecalibacterium and Agathobacter were relatively higher before the intervention. Therefore, the present data do not support a conclusion that butyrate production increased; direct measurement of fecal short-chain fatty acids, including butyrate, will be required in future studies.

Table 4. Exploratory genus-level microbiota analysis.

Taxon	Mean difference	Median difference	Direction
Dorea	-0.00525	-0.00443	Higher before
Agathobacter	-0.03186	-0.02287	Higher before
Clostridium sensu stricto 1	0.010009	0.000609	Higher after
Roseburia	0.002826	0.001087	Higher after
Acidaminococcus	-0.00730	-0.00661	Higher before
Faecalibacterium	-0.01226	-0.00891	Higher before

Mean and median differences indicate after-exercise minus before-exercise relative abundance. Findings are descriptive and were not interpreted as evidence of an intervention effect.

Discussion

In this exploratory prospective pre-post pilot study, five patients with PBC completed a 12-week home-based exercise intervention with concurrent clinical and gut microbiota assessments. The main feasibility findings were that all enrolled patients completed the intervention and the 3-month assessment, no exercise-related adverse events occurred, and resistance-exercise adherence was higher than walking-target achievement. The study also generated descriptive clinical and gut microbiota data, but these findings should not be interpreted as evidence of efficacy.

The feasibility and safety findings are clinically relevant because very few previous studies have assessed exercise therapy in patients with PBC. The 100% completion rate and absence of exercise-related adverse events suggest that a carefully supervised home-based program can be implemented in stable outpatients with preserved hepatic reserve. However, the confidence intervals around these feasibility estimates were wide because of the very small sample size. Recruitment yield was modest but sufficient to reach the planned 5-patient pilot target; future studies should refine recruitment pathways, reduce stool-sampling burden where possible, and clarify eligibility criteria.

Resistance exercise adherence was higher than walking-target achievement. Walking can be influenced by weather, fatigue, pruritus, sleep disturbance, comorbidities and daily schedule, whereas brief resistance exercises can be performed indoors and may be easier to maintain. A future controlled study should therefore include symptom-adjusted goals, feasible resistance exercise modules, and regular behavioral support to improve walking adherence.

The descriptive decrease in total bilirubin requires cautious interpretation. Bilirubin is an important marker of cholestasis and prognosis in PBC, and bilirubin values within the normal range may still have prognostic relevance when combined with ALP normalization [1,13,21]. In the present study, total bilirubin decreased from a median of 0.8 mg/dL at baseline to 0.6 mg/dL at 3 months, and all five patients showed lower values at 3 months than at baseline. However, baseline values were already low, the absolute change was small and the study had no control group. Therefore, this observation should be regarded as a descriptive signal that warrants evaluation in future controlled studies, not as evidence that exercise directly reduced bilirubin.

One possible hypothesis is that exercise may influence cholestasis-related parameters through the hepatobiliary-gut axis. Physical activity has been proposed to affect intestinal motility, gut

304 barrier function, bile acid metabolism, microbial metabolites and systemic inflammation [9].
305 Exercise-related changes in bile acid balance and gut microbiota have also been reported in
306 metabolic liver disease or non-PBC populations [7,10,11]. Nevertheless, findings from
307 nonalcoholic fatty liver disease or sedentary adults cannot be directly extrapolated to PBC, which
308 involves cholangitis, autoimmunity, UDCA treatment and, in some patients, AIH overlap and
309 immunosuppressive therapy. The present study did not directly measure bile acid fractions,
310 short-chain fatty acids, including fecal butyrate, intestinal permeability or inflammatory
311 mediators.
312 The butyrate-related hypothesis is biologically plausible but remains unproven in this study.
313 Butyrate-producing bacteria, including Roseburia and Faecalibacterium, contribute to short-chain
314 fatty acid production in the gut [25-27], and gut microbiota-derived butyrate has been implicated
315 in immune and metabolic reprogramming in experimental PBC-like models [4]. In the present
316 study, however, the direction of change was mixed: Roseburia was relatively higher after the
317 intervention, whereas Faecalibacterium and Agathobacter were relatively higher before the
318 intervention. Thus, the observed pattern should be framed only as a rationale for future fecal
319 metabolomic or targeted short-chain fatty acid analysis, not as evidence that exercise increased
320 butyrate production in PBC.

321 The microbiota findings were descriptive and inconclusive, which is not unexpected in a 5-
322 patient study. The analyses used established QIIME 2 and DADA2 workflows for sequence
323 processing and amplicon sequence variant inference, SILVA for taxonomic assignment, and
324 PICRUSt2 for predicted functional profiling [17-20]; however, these approaches remain
325 constrained by sample size, 16S rRNA-based taxonomic resolution and indirect functional
326 inference. PBC-associated dysbiosis and experimental PBC-like phenotypes have been reported

[2-6,22], but gut microbiota composition varies substantially among individuals and is affected by diet, bowel habits, medications, season and lifestyle. No genus-level or pathway-level finding was interpreted as evidence of an intervention effect, and 16S rRNA sequencing cannot reliably infer species, strain or metabolic activity. PICRUSt2 similarly provides predicted functional profiles rather than direct measurements of genes, transcripts or metabolites.

This study has several limitations. First, the sample size was only five patients, resulting in limited precision. Second, the absence of a control group prevents separation of intervention effects from time effects, regression to the mean, attention effects or natural variability. Third, patients with PBC alone and PBC/AIH overlap were analyzed together despite differences in disease biology and treatment background. Fourth, diet, bowel habits, medications, supplements and other microbiota-related confounders were not standardized; therefore, the findings should be framed as exercise-based supportive care rather than direct evidence for nutritional therapy. Fifth, 16S rRNA sequencing and PICRUSt2 do not provide species-level, strain-level or direct metabolic evidence, including direct evidence of fecal butyrate production. Sixth, adherence was assessed using diaries and activity meter records, but the intensity and quality of each resistance exercise session could not be fully verified in the home setting. Seventh, the progression criteria reported here are pragmatic feasibility benchmarks for planning a future trial and should not be interpreted as evidence that clinical efficacy has been established.

Despite these limitations, the study prospectively combined a home-based exercise intervention, serial clinical measurements, adherence monitoring, quality-of-life assessment and stool microbiota analysis in patients with PBC. The progression benchmarks were met for recruitment of the planned pilot sample, completion, follow-up and safety, and resistance-exercise adherence

was acceptable; however, walking adherence did not meet the desired benchmark and needs refinement before progressing to a larger controlled multicenter study.

Conclusions

A 12-week home-based exercise program was feasible in this 5-patient PBC pilot study with respect to recruitment of the planned pilot sample, intervention completion, follow-up attendance and absence of exercise-related adverse events. Walking adherence was below the desired benchmark, indicating a key area for protocol refinement. The study was accompanied by maintained body weight, small numerical increases in SMI in some patients, and a descriptive decrease in total bilirubin over time; however, these clinical and microbiota findings should be interpreted as exploratory and hypothesis-generating. A larger controlled study incorporating PBC-specific quality-of-life instruments, metagenomics, bile acid and short-chain fatty acid profiling, including fecal butyrate measurement, immune assessments and detailed adherence monitoring appears warranted after refinement of recruitment and adherence-support procedures.

List of abbreviations

AIH: autoimmune hepatitis; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CI: confidence interval; CLDQ: Chronic Liver Disease Questionnaire; gamma-GTP: gamma-glutamyl transpeptidase; PBC: primary biliary cholangitis; SMI: skeletal muscle index; UDCA: ursodeoxycholic acid.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Niigata University (approval number: 2023-0009). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Individual participant data used in this study are not publicly available because of ethical restrictions and privacy protection. De-identified data may be available from the corresponding author upon reasonable request and within the limits permitted by the ethics approval. The availability or deposition status of de-identified 16S rRNA sequencing data will be provided during submission or revision if required by the journal.

Competing interests

T.A., K.O. and M.T. are employees of Miyarisan Pharmaceutical Co., Ltd. K.K. serves as Guest Editor for the Special Issue “Nutritional Support for Improving the Life Quality in Liver Disease”; this role is not related to Pilot and Feasibility Studies and he will not participate in editorial handling or decision-making for this submission. The other authors declare that they have no competing interests. Employees of Miyarisan Pharmaceutical Co., Ltd. contributed to microbiota-related analysis and interpretation as described in the Authors' contributions section.

Funding

This research was funded in part by a Grant-in-Aid for Research on Hepatitis from the Japan Agency for Medical Research and Development (AMED), grant number 24fk0210128h0002.

The funding agency had no role in the design, execution, interpretation, writing of the study, or decision to submit the manuscript for publication.

Authors' contributions

H.K., Y.H., M.K., T.T. and S.T. contributed to conceptualization. H.K., Y.H., M.K., T.T., T.A., K.O. and M.T. contributed to methodology. S.E., S.M., H.N., H.M., S.Y., M.Ku., T.Y., N.K., K.T., H.A. and K.K. contributed to investigation. S.E. and H.K. curated the data and performed formal analysis. S.E. and H.K. drafted the manuscript. All authors contributed to review and editing. H.K. and S.T. supervised the study and acquired funding. All authors read and approved the final manuscript.

Acknowledgements

The authors thank TechnoSuruga Laboratory Co., Ltd. (Shizuoka, Japan) for technical assistance with gut microbiota analysis.

Authors' information

Not applicable.

References

1. Tanaka A, Ma X, Takahashi A, Vierling JM. Primary biliary cholangitis. Lancet. 2024;404:1053-1066.

2. Tang R, Wei Y, Li Y, Chen W, Chen H, Wang Q, et al. Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. Gut. 2018;67:534-541.

3. Li B, Zhang J, Chen Y, Wang Q, Yan L, Li X, et al. Alterations in microbiota and their metabolites are associated with beneficial effects of bile acid sequestrant on icteric primary biliary cholangitis. Gut Microbes. 2021;13:1946366.

4. Wang R, Li B, Huang B, Chen Y, Zhang J, Chen L, et al. Gut microbiota-derived butyrate induces epigenetic and metabolic reprogramming in myeloid-derived suppressor cells to alleviate primary biliary cholangitis. Gastroenterology. 2024;167:733-749.e3.

5. Jiang H, Yu Y, Hu X, Wang J, Chen Y, Zhang J, et al. The fecal microbiota of patients with primary biliary cholangitis causes PBC-like liver lesions in mice and exacerbates liver damage in a mouse model of PBC. Gut Microbes. 2024;16:2383353.

6. Liu Q, Huang B, Zhou Y, Wang R, Li B, Zhang J, et al. Gut microbiome pattern impacts treatment response in primary biliary cholangitis. Med (N Y). 2025;6:100504.

7. Cheng R, Wang L, Le S, Yang Y, Zhao C, Zhang X, et al. A randomized controlled trial for response of microbiome network to exercise and diet intervention in patients with nonalcoholic fatty liver disease. Nat Commun. 2022;13:2555.

8. Terai S, Kamimura H, Hiasa Y, Kawaguchi T, Shimizu M, Yoshiji H, et al. Guidance for liver rehabilitation in chronic liver disease. Hepatol Res. 2026;56:279-291.

9. Molina-Molina E, Lunardi Baccetto R, Wang DQH, de Bari O, Krawczyk M, Portincasa P. Exercising the hepatobiliary-gut axis: the impact of physical activity performance. Eur J Clin Invest. 2018;48:e12958.

10. Zhang M, Xiao B, Chen X, Li H, Yang M, Liu J, et al. Physical exercise plays a role in rebalancing the bile acids of enterohepatic axis in non-alcoholic fatty liver disease. Acta Physiol (Oxf). 2024;240:e14065.

11. Allen JM, Mailing LJ, Niemiro GM, Moore R, Cook MD, White BA, et al. Exercise alters gut microbiota composition and function in lean and obese humans. Med Sci Sports Exerc. 2018;50:747-757.

12. Freer A, Williams FR, Durman S, Abbas N, Taylor-Robinson SD, Jones DEJ, et al. A home-based exercise programme attenuates fatigue in primary biliary cholangitis: results from the EXCITED clinical trial. JHEP Rep. 2024;6:101210.
13. Research Group for Intractable Hepato-Biliary Diseases, Policy Research Project for Intractable Diseases, Ministry of Health, Labour and Welfare of Japan. Clinical practice guidelines for primary biliary cholangitis (2023). Published March 2023. Accessed 7 May 2026.
14. Chazouilleres O, Wendum D, Serfaty L, Montembault S, Rosmorduc O, Poupon R. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology. 1998;28:296-301.
15. Takahashi S, Tomita J, Nishioka K, Hisada T, Nishijima M. Development of a prokaryotic universal primer for simultaneous analysis of bacteria and archaea using next-generation sequencing. PLoS One. 2014;9:e105592.
16. Hisada T, Endoh K, Kuriki K. Inter- and intra-individual variations in seasonal and daily stabilities of the human gut microbiota in Japanese. Arch Microbiol. 2015;197:919-934.
17. Bolyen E, Rideout JR, Dillon MR, Bokulich NA, Abnet CC, Al-Ghalith GA, et al. Reproducible, interactive, scalable and extensible microbiome data science using QIIME 2. Nat Biotechnol. 2019;37:852-857.
18. Callahan BJ, McMurdie PJ, Rosen MJ, Han AW, Johnson AJ, Holmes SP. DADA2: high-resolution sample inference from Illumina amplicon data. Nat Methods. 2016;13:581-583.
19. Quast C, Pruesse E, Yilmaz P, Gerken J, Schweer T, Yarza P, et al. The SILVA ribosomal RNA gene database project: improved data processing and web-based tools. Nucleic Acids Res. 2013;41:D590-D596.

20. Douglas GM, Maffei VJ, Zaneveld JR, Yurgel SN, Brown JR, Taylor CM, et al. PICRUSt2 for prediction of metagenome functions. Nat Biotechnol. 2020;38:685-688.

21. Murillo Perez CF, Harms MH, Lindor KD, van Buuren HR, Hirschfield GM, Corpechot C, et al. Goals of treatment for improved survival in primary biliary cholangitis: treatment target should be bilirubin within the normal range and normalization of alkaline phosphatase. Am J Gastroenterol. 2020;115:1066-1074.

22. Nie Y, Shi Y, Yang Y. Gut microbiota: implications in pathogenesis and potential therapeutic target in primary biliary cholangitis. J Clin Transl Hepatol. 2025;13:776-784.

23. Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. Pilot Feasibility Stud. 2019;5:114.

24. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, Lancaster GA, on behalf of the PAFS consensus group. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot Feasibility Stud. 2016;2:64.

25. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. Environ Microbiol. 2017;19:29-41.

26. Nie K, Ma K, Luo W, Shen Z, Yang Z, Xiao M, et al. Roseburia intestinalis: a beneficial gut organism from the discoveries in genus and species. Front Cell Infect Microbiol. 2021;11:757718.

27. Martin R, Rios-Covian D, Huillet E, Auger S, Khazaal S, Bermudez-Humaran LG, et al. Faecalibacterium: a bacterial genus with promising human health applications. FEMS Microbiol Rev. 2023;47:fuad039.

Figures

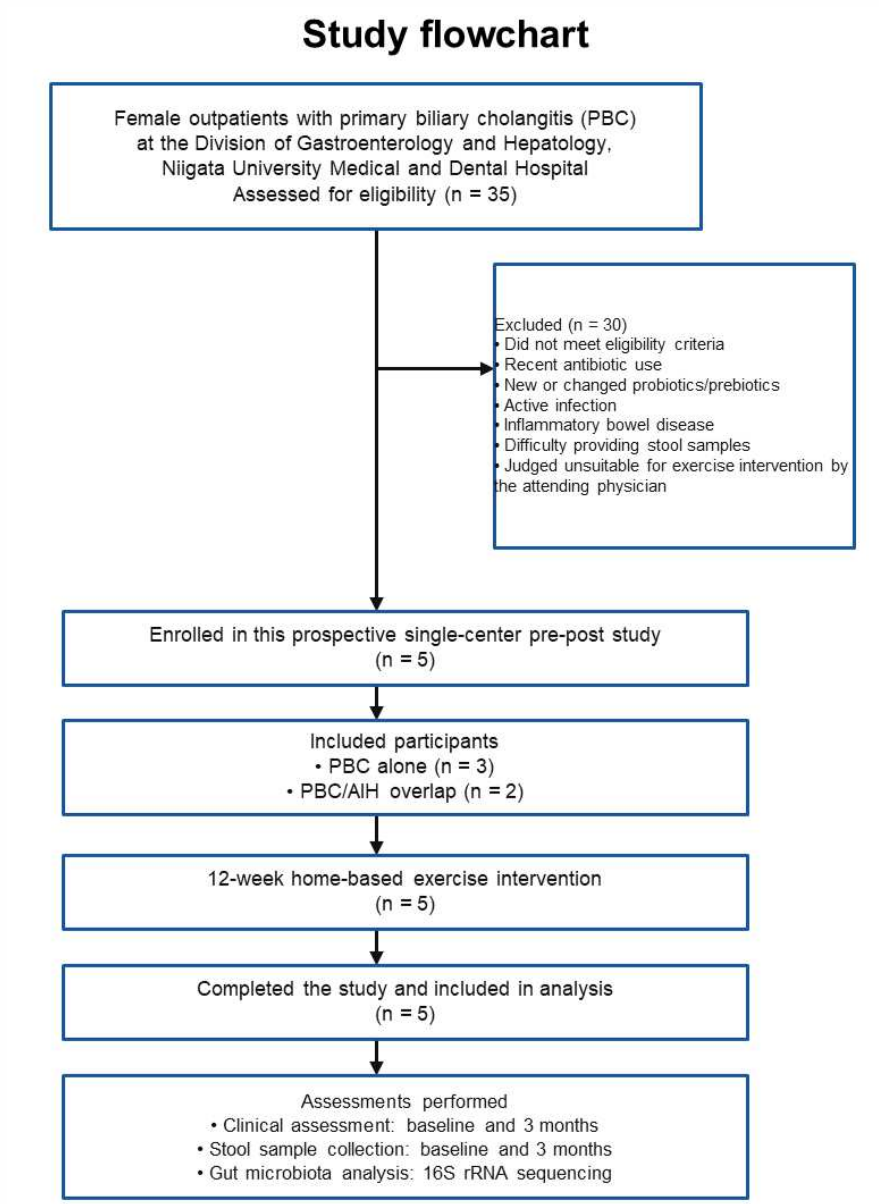


Figure 1. Study flowchart. Female outpatients with PBC were assessed for eligibility, and five patients were enrolled in this prospective single-center pre-post pilot study. All five patients completed the 12-week home-based exercise intervention and were included in the analysis. Clinical assessments and stool sample collection were performed according to the study schedule. AIH autoimmune hepatitis, PBC primary biliary cholangitis.

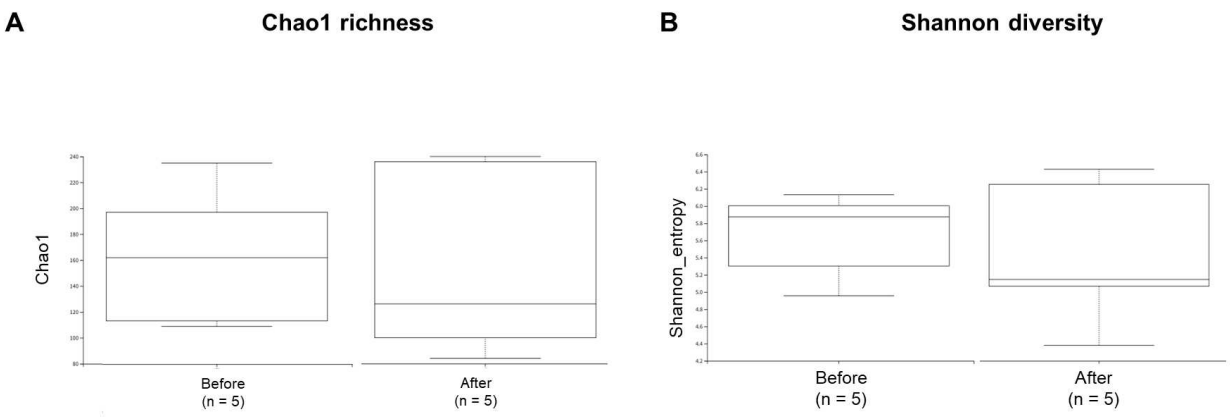
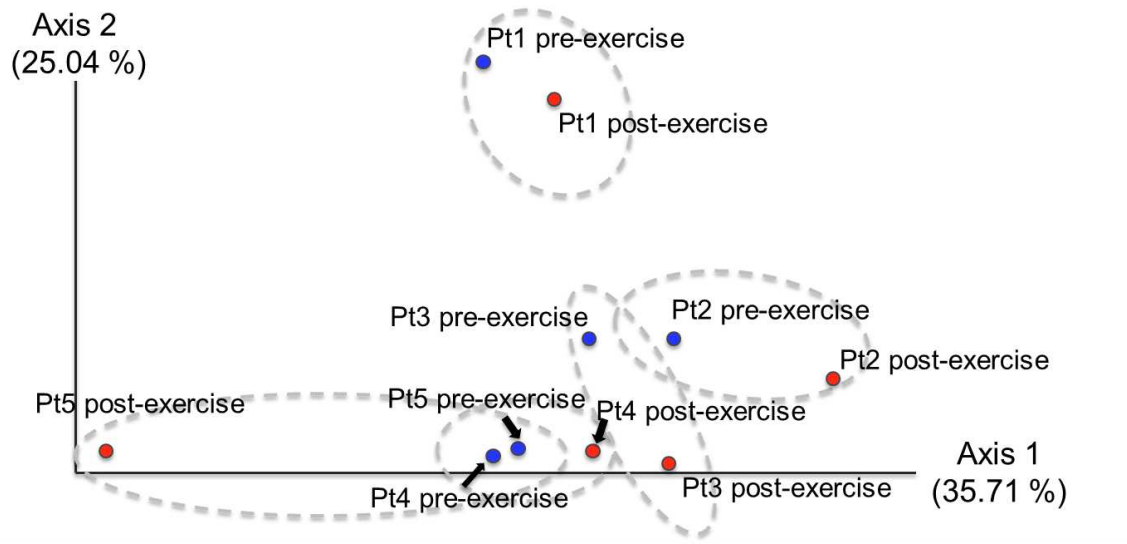


Figure 2. Alpha diversity indices before and after the exercise intervention. Chao1 richness and Shannon diversity were used to evaluate alpha diversity. The distributions are shown descriptively, and no p values are presented.



493

494 Figure 3. Weighted UniFrac-based beta diversity before and after the exercise intervention.

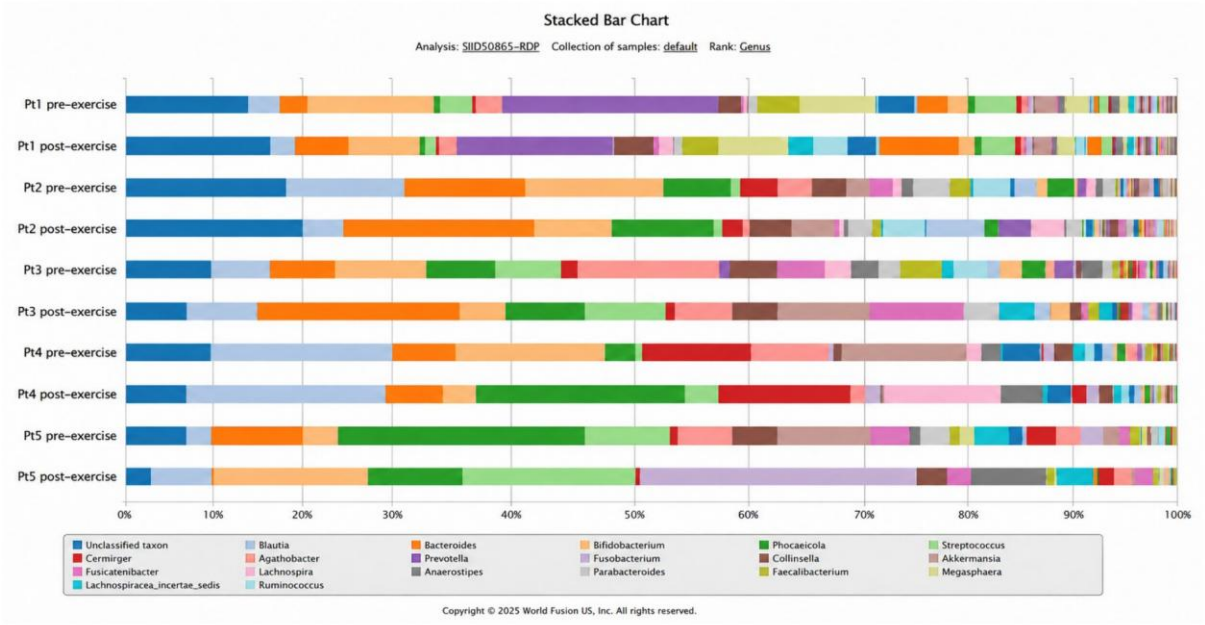
495 Weighted UniFrac analysis was used to evaluate beta diversity by incorporating both

496 phylogenetic distance and relative abundance. No clear pre-post separation was observed after

497 the 12-week intervention. Labels denote paired samples from the five patients before and after

498 exercise.

499



500

501 Figure 4. Genus-level gut microbiota composition before and after the intervention. Genus-level

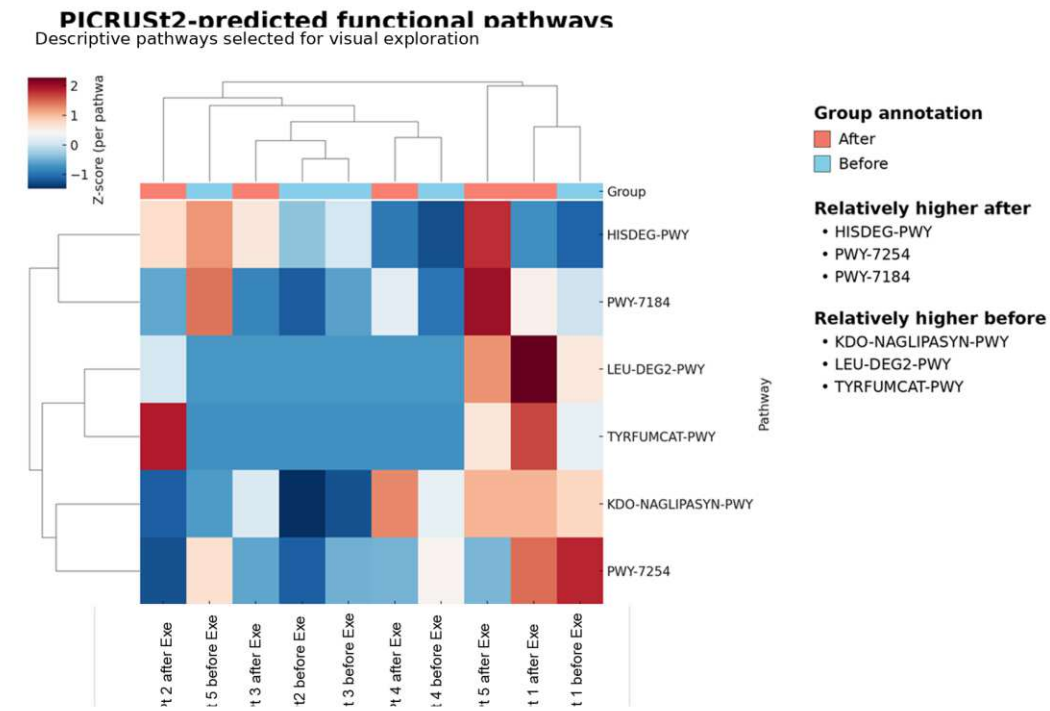
502 microbiota composition is shown for all five patients before and after the intervention.

503 Exploratory genus-level analysis identified taxa with relatively large numerical changes;

504 however, these findings were descriptive only. Because the analysis was based on 16S rRNA

505 sequencing, species-level or strain-level interpretation should be avoided.

506



Descriptive pathway-level heatmap; PICRUSt2 provides predicted functional profiles derived from 16S rRNA data.

Figure 5. PICRUSt2-predicted functional pathway analysis. PICRUSt2 was used to infer functional pathways from 16S rRNA gene sequencing data. Pathways selected for descriptive visualization are shown for hypothesis generation only; PICRUSt2 provides predicted functional profiles and does not directly measure genes, transcripts or metabolites.