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Modular multimodal hospital-home chain physical activity rehabilitation programme (3M2H-PARP) in liver cancer: a protocol for a randomised controlled trial

Haiyan Chen,[1,2] Hanxiao Lu,[1,2] Huimin Zhou,[1,2] Bo Wu,[1,2] Zhixia Dong,[1] Shuo Zhang,[1] Yuanlong Gu,[1] Guangwen Zhou,[3] Jie Xiang,[4] Jun Yang [1]

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HC, HL and HZ are joint first authors.

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[1]Department of General Surgery, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu, China
[2]School of Medicine, Jiangnan University, Wuxi, Jiangsu, China
[3]Department of General Surgery, Shanghai Sixth People's Hospital, Shanghai, China
[4]Department of Endocrinology, Wuxi Mingci Cardiovascular Hospital, Wuxi, Jiangsu, China

Correspondence to
Dr Jun Yang;
wxdoctory@yeah.net

ABSTRACT

Introduction Patients with liver cancer are susceptible to experiencing a decline in muscle mass and function, which can lead to physical frailty and have a negative impact on prognosis. However, there is currently a lack of physical activity interventions specifically tailored for these patients. Therefore, we have developed a modular multimodal hospital-home chain physical activity rehabilitation programme (3M2H-PARP) designed specifically for patients with liver cancer undergoing transarterial chemoembolisation (TACE). We aim to validate the effectiveness and feasibility of this programme through a randomised controlled trial (RCT).

Methods and analysis 3M2H-PARP RCT will compare a 12-week, modular, multimodal physical activity rehabilitation programme that includes supervised exercise in a hospital setting and self-management exercise at home. The programmes consist of aerobic, resistance, flexibility and balance exercise modules, and standard survivorship care in a cohort of liver cancer survivors who have undergone TACE. The control group will receive standard care. A total of 152 participants will be randomly assigned to either the 3M2H-PARP group or the control group. Assessments will be conducted at three time points: baseline, after completing the intervention and a 24-week follow-up visit. The following variables will be evaluated: liver frailty index, Functional Assessment of Cancer Therapy-Hepatobiliary subscale, Cancer Fatigue Scale, Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale and physical activity level. After the completion of the training programme, semi-structured interviews will be conducted with participants from the 3M2H-PARP group to investigate the programme's impact on their overall well-being. SPSS V.26.0 software will be used for statistical analyses.

Ethics and dissemination Ethical approval has been granted by the Jiangnan University School of Medicine Research Ethics Committee. The findings will be disseminated through publication in a peer-reviewed journal.

Trial registration number ChiCTR2300076800.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Modular multimodal hospital-home chain physical activity rehabilitation programme (3M2H-PARP) is a life-cycle exercise rehabilitation regimen tailored for patients with hepatocellular carcinoma treated with transarterial chemoembolisation.
⇒ The 3M2H-PARP encompasses aerobic exercise, resistance training, balance exercises and flexibility training modules for continuous exercise rehabilitation from hospital to home care.
⇒ The development of 3M2H-PARP involved extensive literature review, patient preference surveys and expert consultations.
⇒ The long-term effectiveness of the 3M2H-PARP has not been verified through tracking and follow-up.
⇒ The sample is restricted to a single urban area, which could restrict its generalisability.

INTRODUCTION

Liver cancer is a prevalent malignancy, ranking as the sixth most common cancer globally and the third leading cause of cancer-related deaths.[1] Specifically, hepatocellular carcinoma (HCC) represents the primary type. Liver cancer is a leading cause of cancer deaths globally, ranking in the top three causes in 46 countries and the top five in 90 countries. Predictions suggest a 55.0% increase in new cases by 2040, reaching 1.4 million diagnoses, and a 56.4% rise in deaths, totaling 1.3 million in 2040.[2] A systematic review,[3] comprising 260 studies from 50 countries, revealed that 56% of cases of HCC were associated with hepatitis B virus, while 20% were linked to hepatitis C virus. Therefore, the development of liver cancer is closely correlated with viral infections. Over the past decade, there has been a concomitant increase in the prevalence of metabolic dysfunction-associated steatotic liver disease, as well as global rates of obesity and diabetes.[4] This correlation has significantly contributed to the rapid rise in liver cancer

incidence worldwide, including in the USA.[5–7] Although the pathogenesis of liver cancer varies depending on potential aetiologies, the typical sequence involves liver injury, chronic inflammation, fibrosis, cirrhosis and liver cancer.[8] Cirrhosis, found in 80%–90% of patients with liver cancer, is the primary risk factor.[8] The advancements in liver cancer diagnosis and treatment technology have significantly improved the overall survival rates of patients. However, only 46% of patients are diagnosed in the early stages, and most patients in the middle and late stages cannot be cured. Even after curative treatment, the 5-year recurrence rate is still as high as 70%.[9] Therefore, most liver cancer survivors will coexist with the disease for the rest of their lives.

Transarterial chemoembolisation (TACE) is a treatment that delivers chemoembolic materials through tumour-feeding arteries, inducing tumour necrosis through ischaemia and anticancer drug effects. TACE is often recommended for patients with large or multiple HCC and is commonly used as a salvage treatment for recurrent cases after radical treatment, as well as an initial treatment for HCC.[10] TACE often leads to postembolisation syndrome, characterised by symptoms such as fever, nausea, vomiting, abdominal pain and liver damage.[10] Moreover, patients undergoing TACE treatment are typically advised to rest. According to Kortebein *et al*,[11] significant skeletal muscle loss can occur due to 10 days of bed rest. These findings suggest a risk of muscle mass loss in patients receiving TACE treatment. In addition, sarcopenia and frailty are prevalent complications observed in patients with liver cancer. Apart from the underlying chronic liver diseases, such as malabsorption, hyperammonemia, metabolic alterations and hormone deficiencies, individuals with HCC may also encounter muscle wasting as a secondary consequence of tumour burden.[12] In recent decades, an increasing number of studies have focused on the impact of sarcopenia in chronic liver diseases and their correlation with prognosis and quality of life.[13–21] The implementation of dietary and exercise interventions is considered a fundamental approach in the management of sarcopenia and frailty.

The American Association for the Study of Liver Diseases and International Clinical Practice Guidelines for Sarcopenia are strongly recommended that all individuals diagnosed with sarcopenia receive personalised resistance-based physical activity (PA), tailored to their specific capabilities and preferences.[22–24] Studies have proved that adding exercise to the treatment of cancer and chronic liver disease is safe and feasible.[25–28] PA refers to any form of activity involving skeletal muscle contractions that result in higher energy expenditure than resting metabolism. As a subset of PA, exercise specifically denotes structured, planned and repetitive activities.[29] The primary goal of PA interventions in patients with liver cancer is to optimise muscle quality and function, prevent further skeletal muscle breakdown, enhance cardiovascular adaptability and promote independent performance of daily activities. However, compared with individuals with other chronic diseases, patients with liver cancer typically exhibit lower levels of overall PA. The underlying reasons for this situation are multifaceted and complex. Specifically, it primarily affects patients in the decompensated stage, including inadequate energy and protein intake; physical limitations caused by ascites and lower limb oedema; compensatory events resulting from frequent hospitalisations as well as hepatic encephalopathy (HE) and depressive emotions experienced by the patients. Ultimately, sedentary behaviour leads to further physical function deterioration, resulting in a subsequent decline in quality of life and poor prognosis.[30]

It is noteworthy that the majority of studies on PA intervention for malignant tumours have primarily focused on patients with relatively favourable prognoses, such as breast cancer, prostate cancer and colorectal cancer.[28] Therefore, the PA guidelines derived from these studies may not apply to patients with advanced liver cancer. Therefore, this study designed a modular multimodal hospital-home chain physical activity rehabilitation programme (3M2H-PARP) for patients with liver cancer through systematic literature review and cross-sectional survey. A research hypothesis is proposed that 3M2H-PARP can improve the frailty status and enhance health-related quality of life in patients with primary liver cancer receiving TACE treatment, which will be validated through a randomised controlled trial.

Objectives

This study developed a tailored 3M2H-PARP for patients undergoing TACE HCC. We hypothesised that implementing 3M2H-PARP would lead to an improvement in the Liver Frailty Index (LFI) of patients with HCC compared with standard therapeutic care.

Secondary aims are as follows:

- To examine the effect of 3M2H-PARP intervention on self-reported quality of life among individuals with liver cancer.
- To investigate the effect of 3M2H-PARP intervention on fatigue experienced by patients with liver cancer.
- To explore the influence of 3M2H-PARP intervention on sleep disorders in individuals diagnosed with liver cancer.
- To assess the effects of 3M2H-PARP intervention on anxiety and depression levels in patients with liver cancer.
- Qualitative interviews were conducted to gain insights into how the 3M2H-PARP intervention affected participants' health and overall well-being.

METHODS AND ANALYSIS

Study design

3M2H-PARP is a prospective randomised parallel two-arm controlled trial. Participants who consent to take part in the trial will be randomly assigned to either the control group or the 3M2H-PARP group using a computer program (SPSS V.26.0). The intervention group will

receive a 12-week plan of 3M2H-PARP intervention, while the control group will receive standard care.

Participants

This study aims to enrol 152 participants (76 per arm) with a histological diagnosis of liver cancer and who have undergone TACE. Eligible participants must be aged >18 years, have not engaged in regular exercise (aerobic or resistance training twice or more per week) in the past 3 months and obtain consent from their physician. Exclusion criteria include having a model for end-stage liver disease (MELD) score >15 or being classified as Child-Pugh class C, experiencing oesophageal gastric variceal bleeding within the last 3 months, having malignant ascites, HE, severe heart failure or respiratory failure, hepatic carcinoma with bone metastasis, other limitations on PA and musculoskeletal diseases of the nervous system. All participants will be required to provide written informed consent.

Recruitment and screening

The research team members will identify potential participants from the hospital's clinical database. A written medical certificate, provided by the responsible physician of each participant, will be a prerequisite for inclusion in the study. The research team members will conduct interviews with patients who meet the criteria, provide them with a subject information booklet outlining the study's purpose and specific protocol and assess their interest in participation to determine their willingness to take part. Those expressing interest in participating will undergo a screening assessment, provide written informed consent and complete baseline assessment data collection. The flow chart illustrating participant recruitment from the Affiliated Hospital of Jiangnan University is presented in figure 1.

Randomisation and blinding

Following completion of the baseline assessment, participants will be officially enrolled in the trial and randomly allocated in a 1:1 ratio to either the intervention group receiving 3M2H-PARP or the control group receiving standard care. Block randomisation will be performed using a computer-generated randomisation sequence. The consultant overseeing research methodology and randomisation will remain blind to patient contact. An impartial nursing assessor, adhering to the design of 3M2H-PARP, will evaluate the research interventions without engaging in project implementation. Blinding methods for researchers or participants are not feasible in this study.

Intervention

The 3M2H-PARP intervention will be implemented in the Intervention Department of the Affiliated Hospital of Jiangnan University. The programme is scheduled to last for a duration of 12 weeks and comprises two main components. In the initial stage, a multidisciplinary team consisting of professionals in exercise physiology, oncology, hepatology and nursing will perform a thorough evaluation of the patients. Together, they will establish individualised short-term and long-term objectives, as well as develop tailored exercise regimens for each participant, as outlined in table 1.

Tailored modular multimodal physical activities, including aerobic exercises, resistance training, balance exercises and flexibility exercises, will be customised based on the unique conditions of each patient. These personalised exercise regimens will be developed by exercise physiology specialists or nursing professional (table 2). Throughout their hospital stay, patients will receive one-on-one supervised exercise guidance daily. Additionally, patients are encouraged to wear an exercise bracelet that monitors their physiological condition and tracks their exercise volume during workouts. They are also advised to maintain a diet and exercise diary. Subsequent stage goals will be set based on feedback received from patients. The content of the 3M2H-PARP intervention adheres strictly to established guidelines for exercising among patients with cancer,[25 28 31] as well as expert consensus for patients with cirrhosis.[26 30 32] This endeavour seeks to go beyond the confines of a hospital-centred supervised exercise regimen by implementing remote monitoring via a home-based programme. Its principal goal is to encourage autonomous lifestyle modifications that boost physical capabilities and enhance general well-being. The progress of the study is depicted in figure 2.

In the 3M2H-PARP intervention, one-on-one in-hospital supervised exercises were used to ensure safety and appropriate techniques for all exercises and to determine training load for subsequent sessions. Specifically, the intensity of aerobic exercise will be tailored based on participants' physical fitness levels. During the compression of the femoral artery by a hemostatic device after TACE, the operated limb should be kept straight. While lying in bed, patients should be instructed to perform ankle pump exercises and muscle pump exercises. Twelve hours postoperatively, patients should be encouraged to mobilise to prevent deep vein thrombosis formation. Patients will be encouraged to initiate progressive walking exercises in the ward corridors starting from day 1 after TACE, with durations ranging from 5 min. The exercise intensity will be determined using the reserve heart rate (HRR) calculated by the Karvonen formula (HRR=maximum heart rate−resting heart rate), targeting an intensity range of 50%–80% of HRR.[33] Participants will wear a Huawei exercise bracelet (WATCH FIT 2) to monitor their heart rate and ensure adherence to prescribed exercise intensities. Additionally, intensity levels will also be assessed using the Borg rating of perceived exertion (RPE).[34 35] Assign an RPE score of 5–6 out of 10, and it can also use a conversation test to see how hard you are trying.[22] It is advisable for individuals to be able to converse during PA, even if they experience slight breathlessness, while progressively enhancing the frequency and duration of aerobic exercise at a safe intensity level. Walking is widely preferred by various patients with cancer due to its simplicity and accessibility as an effective form of aerobic activity. Moreover, alternative aerobic exercise

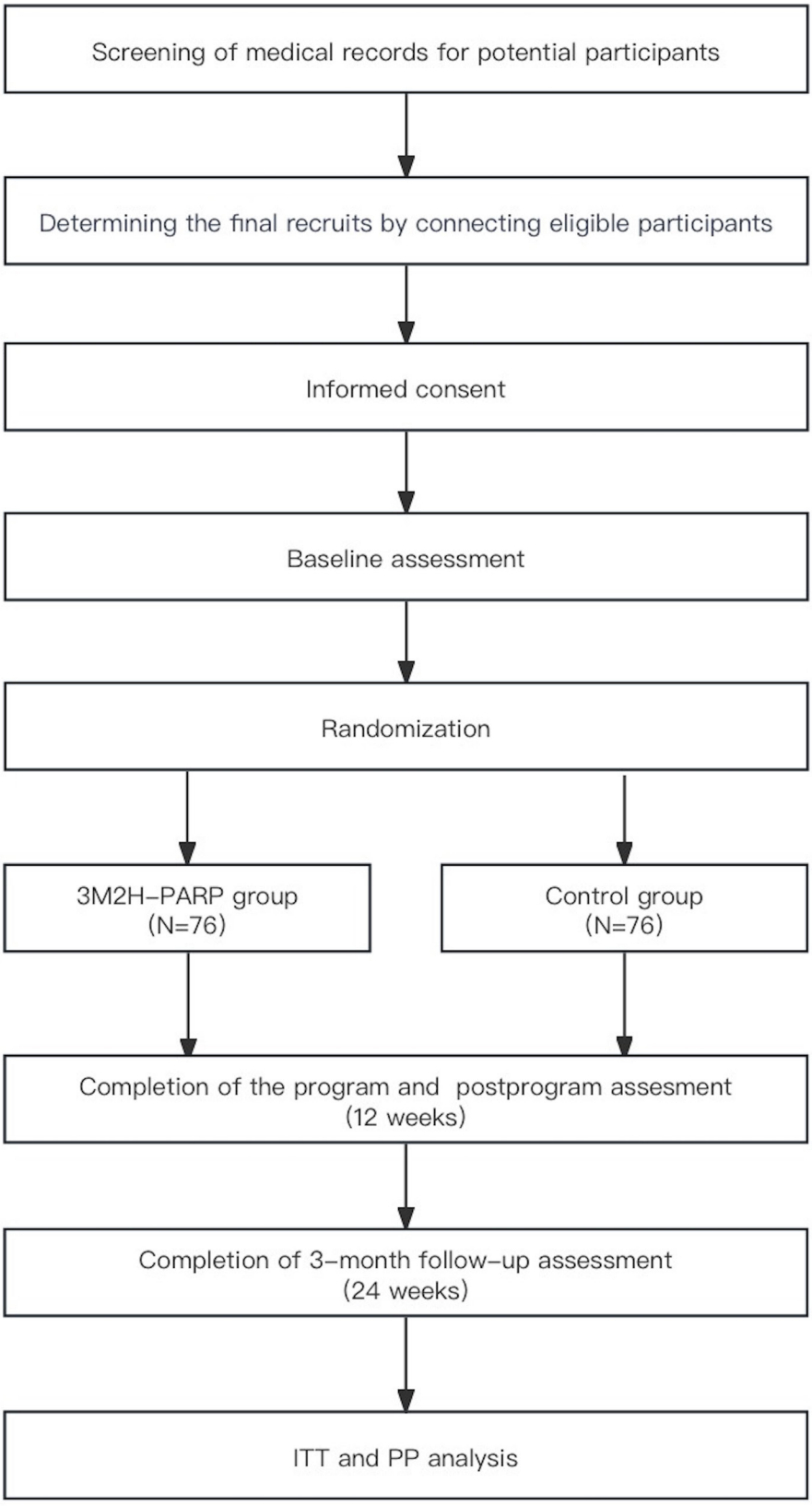

Figure 1 Participant flow through the study. Eligible patients consenting to participate will undergo baseline assessments and be randomly assigned to either the 3M2H-PARP group (n=76) or the control group (n=76). The 3M2H-PARP group will complete a modular multimodal from hospital (T1) to home (T2) physical activity rehabilitation programme. Follow-up assessments for all participants will occur at 12 and 24 weeks post-trial completion. Analysis will be by ITT. ITT, intention to treat. PP, per protocol.

Table 1 3M2H-PARP intervention prescription

Exercise modular	Frequency (week)	Intensity	Start and aim	Progression
Aerobic	4–7 days	Moderate intensity: 50%–80% HRR or 5–6 on Borg Scale (out of 10)	Start: from 5 to 40 min per session Aim: 150 min per week	Keep advancing to keep yourself to stay at a Borg Scale 5–6 out of 10 during the activity.
Resistance	2–4 days	Focus on maintaining good form to work the desired muscle groups. Ensure that the muscles feel slightly fatigued at the end of each set	Start: 3–4 exercises per session One set of 10–15 repetitions Start at P0 level, then move to theraband, and then to light weights (1–3 pounds to start) Aim: all six exercises per session Three sets of 10–15 repetitions	Gradually increase the number of sets, starting from 2 sets and gradually increasing to 3 sets, while maintaining a comfortable range of 10–15 repetitions each time. Once successfully completing three sets, progress to the next level with confidence and achieving strength and stability.
Flexibility	At least 2 days	Hold the stretch position until there is a feeling of slight discomfort; do not overstretch the muscle	One set of three repetitions Hold each stretch for 20–30 s	Progress to the next level when you feel confident, strong and stable.
Balance	At least 2 days	Using multiple muscle groups, the aim here is to hold the position and remain steady	One set of three repetitions	Progress to the next level when you feel confident, strong and stable.

HRR, reserve heart rate; 3M2H-PARP, modular multimodal hospital-home chain physical activity rehabilitation programme.

categories like yoga, Tai Chi and Baduanjin can be customised based on personal preferences. Our goal is to be able to engage in 150 min of moderate-intensity aerobic activity per week. The resistance training programme is designed to progress from lighter loads with higher repetitions towards heavier loads with fewer repetitions. Specifically, exercises will transition from bodyweight movements to incorporating resistance bands or dumbbells at varying levels of resistance. For increased difficulty, sets may be increased up to 2–3 sets with each set easily repeated for 10–15 repetitions. Gradual increments in elastic band or dumbbell weight by 1–2 pounds at a time are recommended.[36] The initial stage of balance exercise may involve static exercises, such as standing on one foot with the support of a hand chair to ensure safety. Subsequently, individuals can attempt closing their eyes and aim to maintain this position for 20–30 s. Dynamic balance exercises can then be introduced, such as walking in a straight line with a narrow gait or attempting to align the front heel against the tip of the back foot while maintaining a safe and stable posture. To improve flexibility, individuals with weaker physical strength can opt for seated static stretches targeting shoulders, elbows, lower back and legs (eg, sitting stretches, side bends, chest stretches). Those with better physical strength can perform standing static stretches (eg, toe touch, calf stretch, shoulder stretch triceps stretch) until experiencing mild discomfort without overstretching muscles. It is recommended that balance and flexibility exercises are performed at least twice a week until you feel confident, strong and stable enough to progress further. Additionally, before discharge from the hospital, it is important to ensure that patients and their families can master simple comprehensive sports activities which they can adjust according to their circumstances in terms of frequency and intensity. On being discharged from the hospital, patients will receive modest and practical items such as elastic bands and dumbbells as parting gifts.

Overcoming barriers to exercise

The Fogg Behaviour Model (www.BehaviorModel.org) proposes that individuals need three crucial factors to achieve a particular behaviour: motivation, ability to perform the behaviour and a trigger that is later refined as a prompt. It is only when all these elements are simultaneously fulfilled that they can effectively encourage the desired behaviour; otherwise, it will not occur spontaneously. The acronym B=MAP represents this concept. Motivational interviewing employs an empathetic and non-confrontational approach to clinical interaction to facilitate behavioural change. Within this interaction, patients assume the role of equal partners.[37] This effective technique uses open-ended questions to jointly explore patients' readiness for change, motivation, confidence and conflict resolution. It emphasises autonomy while fostering positive emotions through support from our team and their families, instilling a sense of hope and belonging. In terms of capability, professional exercise physiology specialists and nurses provide daily skill training during hospitalisation along with exercise manuals and video materials, aiming to initiate exercise from the introduction level so that participants can actively engage. To facilitate prompts, we equip patients with wearable activity monitors that offer real-time data on daily step count, calorie expenditure and sedentary-to-moderate

Table 2 3M2H-PARP guidance for resistance, flexibility and balance

Resistance activities—start with one set of 10–15 repetitions	
Shoulders	P0: lateral arm raises P1: lateral arm raises with banding P2: lateral arm raises with free weights
Biceps	P0: arm curls with light or no weights P1: arm curls with banding P2: arm curls with free weights
Triceps	P0: seated triceps extension with banding P1: overhead triceps extension with banding P2: overhead triceps extension with free weights
Quadriceps	P0: seated leg extensions P1: seated leg extensions with banding P2: seated leg extensions with banding (higher resistances)
Lower leg	P0: seated calf raises P1: standing calf raises P2: standing calf raises with banding
Multijoint	P0: chair sit to stand P1: wall squat P2: squat with hand-held free weights
Flexibility: one set of three repetitions	
P0	Simple range of motions for shoulders, elbows, lower back and knees to static stretches that can be performed seated in a chair (eg, chair sit and reach, lateral side bends, chest stretch)
P1	Standing static stretches (eg, toe touch, calf stretch, shoulder stretch, triceps stretch, chest stretch)
P2	Floor and standing stretches (eg, hurdler's stretch, calf stretch, wrist stretch, shoulder and chest stretch)
Balance: one set of three repetitions	
P0	Single leg raises with assistance of a chair
P1	Single leg raises with assistance of a chair and eyes are closed
P2	Dynamic balance: walking in a straight line with a narrow gait

3M2H-PARP, modular multimodal hospital-home chain physical activity rehabilitation programme; P0, introduction level; P1, progression level 1; P2, progression level 2.

exercise ratio. When the sedentary time reaches 40 min, the wearable device automatically sends a reminder. Simultaneously, wearable devices provide objective PA level and physiological data, thereby establishing a foundation for exercise training. Additionally, weekly telephone follow-up monitoring reminders are provided by our research team.

The participants in the control group will continue to receive standard care and follow-up.

Patient or public involvement

There was no patient or public involvement in the design of the study protocol.

Measures

Frailty

The inclusion of grip strength, chair standing and balance tests in the LFI enhances the validity of the frailty concept and improves risk prediction for mortality while on the waiting list for liver transplantation using MELD Na alone.[21] The LFI test includes three separate assessments. First, grip strength is measured as the average of three trials using a hand dynamometer in the tester's dominant hand. Second, timed chair stands are performed with arms crossed on the chest to measure the time taken for five repetitions. Lastly, balance is assessed by measuring the time taken to maintain three different postures (feet side-by-side, semi-tandem and tandem), with a maximum of 10 s allowed for each posture. By applying the formula LFI=(0.330×sex-adjusted grip strength)+(2.529×chair standing times per second)+(0.040×balance time)+6, results can be calculated at http://liverfrailtyindex.ucsf.edu. Frailty is classified as LFI <3.2, prefrailty falls within the range of 3.2–4.4 LFI units and frailty is defined as an LFI ≥4.5.

Quality of life

Quality of life is considered a crucial patient outcome, as significant as disease-free and overall survival, and should be measured accordingly. Health-related quality of life, a multidimensional patient-reported outcomes measurement method, plays an essential role in assessing tumour results.[38 39] Participants' quality of life was measured on the Functional Assessment of Cancer Therapy-hepatobiliary subscale (FACT-Hep). FACT-Hep is a widely recognised and extensively used quality of life assessment tool for patients with hepatobiliary disease, known for its comprehensive content and international acclaim.[38] The FACT-Hep questionnaire comprises a total of 45 self-reported items, with 27 items from the FACT-General (FACT-G) and 18 items from the Hep. The overall score for FACT-Hep is obtained by summing up the scores from both FACT-G and Hep.[40]

Fatigue

Cancer-related fatigue is a commonly observed symptom that frequently accompanies cancer in patients, exerting a substantial influence on their prognosis and overall well-being. To assess the intensity of fatigue experienced by individuals with cancer, Okuyama *et al*[41] developed the Cancer Fatigue Scale (CFS) in 2000. The scale consisted of 15 items in 3 dimensions: physical fatigue, cognitive fatigue and emotional fatigue. The 5-point Likert scoring method was used, and the higher the total score, the more obvious the fatigue.

Sleep quality

The assessment of sleep quality will be conducted using the Pittsburgh Sleep Quality Index (PSQI), which was compiled by Buysse *et al*,[42] a psychiatrist from the University of Pittsburgh, in 1989. This scale can be used to evaluate the sleep, quality of individuals with sleep disorders

	STUDY PERIOD					
	Screening	Enrolment	Interention		Postintervention	3-Month follow-up
Timepoint	T-1	T0	T1	T2	T3	T4
ENROLLMENT:						
Eligibility screen	×	×				
Informed consent		×				
Medical history		×				
Demographics		×				
Allocation		×				
INTERVENTIONS:						
3M2H-PARP group			●	●		
Control group			×	×		
Adverse event monitor		●	●	●	●	●
ASSESSMENTS:						
Liver frailty index		×			×	×
FACT-Hep		×			×	×
PA level		×			×	×
CFS		×			×	×
PSQI		×			×	×
HADS		×			×	×
Interview			×		×	

Figure 2 Schematic diagram of the study schedule. T1, in the hospital, T2, at home. 3M2H-PARP, modular multimodal hospital-home chain physical activity rehabilitation programme; CFS, Cancer Fatigue Scale; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary; HADS, Hospital Anxiety and Depression Scale; PA, physical activity; PSQI, Pittsburgh Sleep Quality Index.

and mental health conditions, as well as for assessing the sleep quality of the general population. The PSQI assesses the subjects' sleep quality over the past month through a combination of 19 self-rated items and 5 other-rated items, excluding item 19 and the remaining 5 other-rated items from scoring. These items are categorised into seven dimensions: subjective sleep quality, sleep onset latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Total scores range from 0 to 21; higher scores indicate poorer sleep quality.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS), developed by Zigmond and Snaith,[43] is a measurement tool used to assess anxiety and depression levels in participants. It aims to gain insights into patients' psychological well-being by examining these two variables over a period of approximately 1 month, with findings that can be generalised to the general population.

Safety

Patient safety will be crucial for the successful implementation of the 3M2H-PARP intervention. Standard safety measures include a comprehensive pre-exercise assessment conducted by a physician, an exercise physiology specialist and a nurse prior to commencing the trial. All testing evaluations and supervised practice sessions will take place in a ward, ensuring that patients receive appropriate care even after discharge through a progressive movement plan. Additionally, patients will be equipped with wearable devices which will promptly alert healthcare professionals of any signs of change. Real-time data on patient movements will be uploaded to the cloud for continuous monitoring and evaluation purposes. The safety of the trial itself will be assessed by meticulously recording any adverse events that occur during the intervention period. In case of serious adverse events, immediate reporting to the Ethics Committee of the Affiliated Hospital of Jiangnan University is mandatory.

Adherence

Adherence is crucial for ensuring the safety and effectiveness of 3M2H-PARP intervention. On completion, 3M2H-PARP will provide a comprehensive report detailing key metrics, including completion rates of supervised classes and home-based exercise. This assessment will be

based on patients' exercise diaries, where they record daily types and durations of physical activities, as well as changes in their PA levels before and after the intervention. Measuring PA levels poses challenges due to its complex multidimensional nature. Self-report methods like questionnaires are widely used for their simplicity and cost-effectiveness; in this study, international physical activity questionnaire (IPAQ) were employed to measure PA levels before and after interventions in both groups. Accelerometers offer the ability to assess PA behaviour across sedentary to vigorous levels, providing objective data on the frequency, intensity, type and duration of PA. Balancing precision and ease of use, accelerometers are considered the most reliable method for measuring PA in cancer research. In this study, postintervention PA levels will be assessed using the Actigraph GT3X+activity monitor, a widely validated tool in oncology research.[44 45] The compact and lightweight device will be worn on the hip for a duration of seven consecutive days. This compact and lightweight device will be worn on the hip for seven consecutive days to capture habitual PA. The primary accelerometer outcome will be the total weekly minutes of moderate-to-vigorous physical activity (MVPA) in bouts lasting at least 10 min, while secondary outcomes will include total weekly minutes of MVPA, including bouts of <10 min. Binary variables will be generated for each MVPA outcome to indicate 150 min of activity. Data collected will be analysed using Actilife software.

Qualitative data collection

The impact of the 3M2H-PARP intervention on participants' daily lives will be investigated through qualitative research. After the intervention, a semi-structured interview was conducted with participants. To explore the physical, psychological and social impacts of the intervention, an experienced researcher in qualitative research led the semi-structured interview. The collected data were analysed using content analysis to organise and transform them into smaller units for review and scrutiny, followed by coding and classification. Themes were extracted from the data, validated and relationships between themes were established.

Sample size calculation

This research, conducted as a randomised controlled trial, focuses on LFI as the primary outcome. A sample size of 114 participants (57 per group) was determined based on the published literature,[46] assuming a 0.21 increase in LFI in the 3M2H-PARP group compared with controls, with an SD of 0.4. The study aims to achieve 80% statistical power at a significance level of 0.05 (two-sided), with an anticipated 25% attrition rate, leading to the enrolment of 152 participants (76 per group).

Data management

The plan for managing data will outline the procedures for handling data throughout and after the project, which includes documenting evaluation results in a written report and subsequently inputting them into a computer software program that requires a password for access. To ensure accurate input, techniques for validating data will be used, while researchers will personally verify all physical records stored securely in a locked filing cabinet. After the trial is completed, de-identified data will be securely stored in an online repository to comply with requirements for publishing openly accessible content.

Data analysis

The quantitative analysis of data will be conducted using IBM SPSS V.26.0 software. Normally distributed continuous variables will be reported as means (SD), while non-normally distributed data will be presented as median (range). Categorical variables will be displayed as counts and proportions. To model the longitudinal change in the primary response between groups, a linear mixed model will be employed, allowing for missing data through pair-wise deletion and accounting for within-subject correlations across time points. In the case of a normal distribution, a one-way repeated measures will be conducted to examine differences in baseline values. A mixed model will then be applied for each dependent variable (LFI, FACT-Hep score, CFS score, PQSI score, HADS score and PA level), with group (3M2H-PARP and CTRL) and time (0 week, 12 weeks and 24 weeks) as fixed factors while participants are considered random factors. If the data distribution is non-normal, a Kruskal-Wallis test will be employed to assess differences in baseline values. The Friedman test will then be used for analysing repeated measures. To address potential issues related to multiple comparisons during data analysis, adjusted p values will be calculated using Hummel's procedure; both adjusted and non-adjusted values will be reported. Additionally, Cohen's d effect sizes will be computed within groups (0–12 weeks and 0–24 weeks changes) as well as between groups for each outcome. The intention-to-treat group, comprising all patients with analysable data regardless of fidelity, compliance or arm cross-over, will form the primary analysis set. Statisticians will finalise a comprehensive Statistical Analysis Plan before conducting the final T3 visit and remain blinded to the study arm until the completion of the analysis process.

The qualitative data will be analysed using qualitative descriptive methods. The Braun and Clarke six-stage theme analysis method will be employed to analyse all collected data. A team of researchers will analyse all transcripts following a predetermined process.

Study status

Recruitment for the study is currently ongoing. The study officially began on 20 October 2023, with an anticipated completion date of 31 December 2024.

ETHICS AND DISSEMINATION

Ethics

All research content has obtained approval from the Ethics Committee of Jiangnan University School of Medicine, identified by batch number JNU20230301IRB22. Moreover, the study will adhere to the principles set forth in the Declaration of Helsinki. Additionally, the current study is duly registered on the Chinese Clinical Trial Register (https://www.chictr.org.cn/) with registration number ChiCTR2300076800.

Dissemination

The findings of the 3M2H-PARP intervention will be disseminated through peer-reviewed publications and conference presentations. Following the completion of the study, an educational workshop will be conducted to present the results to participants and their families. All data analysis and computer code used in this study will be made available in open access repositories.

Consent or assent

Individuals will receive comprehensive information about the study and participation requirements through written materials and a verbal discussion with a research team member. They will provide written consent after understanding they can withdraw anytime without impacting their care. Eligible participants will review the consent form with a study team member, who will explain procedures, allowing time for full consideration and consultation as needed.

Contributors HC: writing—original draft, investigation, conceptualisation. HL: writing—original draft, investigation. HZ: writing—original draft, methodology. BW: visualisation, software. ZD: writing—review and editing, validation. SZ: validation, investigation. YG: validation, funding acquisition. GZ: validation, supervision. JX: validation, investigation. JY: writing—review and editing, validation, supervision, project administration, funding acquisition, conceptualisation. All authors reviewed the final draft and approved the final manuscript.

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ORCID iD

Jun Yang http://orcid.org/0000-0003-0393-539X

REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
2 Rumgay H, Arnold M, Ferlay J, *et al*. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol* 2022;77:1598–606.
3 Maucort-Boulch D, de Martel C, Franceschi S, *et al*. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer* 2018;142:2471–7.
4 Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. *J Hepatol* 2019;70:531–44.
5 Stepanova M, De Avila L, Afendy M, *et al*. Direct and indirect economic burden of chronic liver disease in the United States. *Clin Gastroenterol Hepatol* 2017;15:759–66.
6 Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2021;18:223–38.
7 Chiang JYL, Li T. Pathogenesis of fatty liver diseases and hepatocellular carcinoma. *Liver Research* 2022;6:201–2.
8 Chidambaranathan-Reghupaty S, Fisher PB, Sarkar D. Hepatocellular carcinoma (HCC): epidemiology, etiology and molecular classification. *Adv Cancer Res* 2021;149:1–61.
9 Lu S-D, Li L, Liang X-M, *et al*. Updates and advancements in the management of hepatocellular carcinoma patients after hepatectomy. *Expert Rev Gastroenterol Hepatol* 2019;13:1077–88.
10 Cho Y, Choi JW, Kwon H, *et al*. Transarterial Chemoembolization for hepatocellular carcinoma: 2023 expert consensus-based practical recommendations of the Korean liver cancer Association. *Clin Mol Hepatol* 2023;29:521–41.
11 Kortebein P, Ferrando A, Lombeida J, *et al*. Effect of 10 days of bed rest on Skeletal muscle in healthy older adults. *JAMA* 2007;297:1772–4.
12 Gallo P, Silletta M, De Vincentis A, *et al*. Sarcopenia in hepatocellular carcinoma: pathogenesis and management. *Chemotherapy* 2022;67:152–63.
13 Cron DC, Friedman JF, Winder GS, *et al*. Depression and frailty in patients with end-stage liver disease referred for transplant evaluation. *Am J Transplant* 2016;16:1805–11.
14 Kang SH, Jeong WK, Baik SK, *et al*. Impact of Sarcopenia on Prognostic value of cirrhosis: going beyond the hepatic venous pressure gradient and MELD score. *J Cachexia Sarcopenia Muscle* 2018;9:860–70.
15 Kim HY, Jang JW. Sarcopenia in the prognosis of cirrhosis: going beyond the MELD score. *World J Gastroenterol* 2015;21:7637–47.
16 Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, *et al*. Inclusion of Sarcopenia within MELD (MELD-Sarcopenia) and the prediction of mortality in patients with cirrhosis. *Clin Transl Gastroenterol* 2015;6:e102.
17 Tandon P, Tangri N, Thomas L, *et al*. A rapid bedside screen to predict unplanned hospitalization and death in outpatients with cirrhosis: A prospective evaluation of the clinical frailty scale. *Am J Gastroenterol* 2016;111:1759–67.
18 Ando Y, Ishigami M, Ito T, *et al*. Sarcopenia impairs health-related quality of life in Cirrhotic patients. *Europ J Gastroenterol Hepatol* 2019;31:1550–6.
19 Guo Y, Ren Y, Zhu L, *et al*. n.d. Association between Sarcopenia and clinical outcomes in patients with hepatocellular carcinoma: an updated meta-analysis. *Sci Rep*13:934.
20 Voron T, Tselikas L, Pietrasz D, *et al*. Sarcopenia impacts on Short- and long-term results of hepatectomy for hepatocellular carcinoma. *Ann Surg* 2015;261:1173–83.
21 Lai JC, Covinsky KE, Dodge JL, *et al*. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017;66:564–74.
22 Dent E, Morley JE, Cruz-Jentoft AJ, *et al*. International clinical practice guidelines for Sarcopenia (ICFSR): screening. *J Nutr Health Aging* 2018;22:1148–61.
23 Chen L-K, Woo J, Assantachai P, *et al*. Asian working group for Sarcopenia: 2019 consensus update on Sarcopenia diagnosis and treatment. *J Am Med Dir Assoc* 2020;21:300–7.
24 Lai JC, Tandon P, Bernal W, *et al*. Malnutrition, Frailty, and Sarcopenia in patients with cirrhosis: 2021 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2021;74:1611–44.
25 Rock CL, Thomson CA, Sullivan KR, *et al*. American Cancer society nutrition and physical activity guideline for cancer survivors. *CA Cancer J Clin* 2022;72:230–62.
26 Tandon P, Ismond KP, Riess K, *et al*. Exercise in cirrhosis: translating evidence and experience to practice. *J Hepatol* 2018;69:1164–77.

27 Wallen MP, Keating SE, Hall A, *et al*. Exercise training is safe and feasible in patients awaiting liver transplantation: A pilot randomized controlled trial. *Liver Transpl* 2019;25:1576–80.
28 Campbell KL, Winters-Stone KM, Wiskemann J, *et al*. Exercise guidelines for cancer survivors: consensus statement from international Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51:2375–90.
29 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985;100:126–31.
30 Brustia R, Savier E, Scatton O. Physical exercise in Cirrhotic patients: towards Prehabilitation on waiting list for liver transplantation. A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2018;42:205–15.
31 Hayes SC, Newton RU, Spence RR, *et al*. The exercise and sports science Australia position statement: exercise medicine in cancer management. *J Sci Med Sport* 2019;22:1175–99.
32 Aamann L, Dam G, Rinnov AR, *et al*. Physical exercise for people with cirrhosis. *Cochrane Database Syst Rev* 2018;12:CD012678.
33 Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn* 1957;35:307–15.
34 Arney BE, Glover R, Fusco A, *et al*. Comparison of RPE (rating of perceived exertion) scales for session RPE. *Int J Sports Physiol Perform* 2019;14:994–6.
35 Scherr J, Wolfarth B, Christle JW, *et al*. Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. *Eur J Appl Physiol* 2013;113:147–55.
36 American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009;41:687–708.
37 Bean MK, Powell P, Quinoy A, *et al*. Motivational interviewing targeting diet and physical activity improves adherence to Paediatric obesity treatment: results from the MI values randomized controlled trial. *Pediatr Obes* 2015;10:118–25.
38 Wohlleber K, Heger P, Probst P, *et al*. Health-related quality of life in primary hepatic cancer: a systematic review assessing the methodological properties of instruments and a meta-analysis comparing treatment strategies. *Qual Life Res* 2021;30:2429–66.
39 Steel JL, Eton DT, Cella D, *et al*. Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. *Ann Oncol* 2006;17:304–12.
40 Heffernan N, Cella D, Webster K, *et al*. Measuring health-related quality of life in patients with hepatobiliary cancers: the functional assessment of cancer therapy-hepatobiliary questionnaire. *J Clin Oncol* 2002;20:2229–39.
41 Okuyama T, Akechi T, Kugaya A, *et al*. Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. *J Pain Symptom Manage* 2000;19:5–14.
42 Buysse DJ, Reynolds CF III, Monk TH, *et al*. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Research* 1989;28:193–213.
43 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
44 Broderick JM, Ryan J, O'Donnell DM, *et al*. A guide to assessing physical activity using Accelerometry in cancer patients. *Support Care Cancer* 2014;22:1121–30.
45 Limb ES, Ahmad S, Cook DG, *et al*. Measuring change in trials of physical activity interventions: a comparison of self-report questionnaire and Accelerometry within the PACE-UP trial. *Int J Behav Nutr Phys Act* 2019;16:10.
46 Siramolpiwat S, Limthanetkul N, Pornthisarn B, *et al*. Branched-chain amino acids supplementation improves liver frailty index in frail compensated Cirrhotic patients: a randomized controlled trial. *BMC Gastroenterol* 2023;23:154.