Walking exercise through smartphone application plus branched-chain amino acid supplementation benefits skeletal muscle mass and strength in liver cirrhosis: A prospective control trial

Gehübungen durch Smartphone-Anwendung plus Supplementierung mit verzweigtkettigen Aminosäuren wirken sich positiv auf die Skelettmuskelmasse und -kraft bei Leberzirrhose aus: Eine prospektive Kontrollstudie

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ABSTRACT

Introduction and objectives Whether a combination of exercise and branched-chain amino acid (BCAA) supplementation was more beneficial than those given alone in sarcopenia related to liver cirrhosis (LC) is unknown. Widely used smartphone applications provide continuous and easily expandable management of chronic liver disease (CLD). This study is to investigate the effects of unsupervised walking exercise using WeChat combined with BCAA supplementation on skeletal muscle mass and strength in LC.

Materials and Methods The 127 LC patients of Child–Pugh A/B were assigned to group A (BCAA supplements, n = 42), group B (walking exercise, n = 43) and group C (walking exercise plus BCAA supplements, n = 42). Laboratory data, average daily steps, serum BCAA, skeletal muscle mass index (SMI) and grip strength were analyzed pre- and 3 months after interventions.

Results Of the 124 patients who completed interventions, albumin and daily steps were significantly increased in all groups ($p = 0.0001$). Post-intervention BCAA were significantly elevated in group A (A vs B, $p = 0.001$) and C (C vs B, $p = 0.012$;). While post-intervention daily steps in group B (B vs A, $p = 0.0001$) and C (C vs A, $p = 0.0001$) were higher. Grip strength (C vs A, $p = 0.020$; C vs B, $p = 0.036$) and SMI (C vs A, $p = 0.035$; C vs B, $p = 0.012$) were increased in group C. Prevalence of sarcopenia was significantly decreased in group C ($p = 0.015$).

Conclusions A combination of unsupervised walking exercise using smartphone applications and BCAA supplementation might be an effective and safe treatment for cirrhosis patients with Child–Pugh A/B to improve skeletal muscle mass and strength or to prevent progress of sarcopenia.

ZUSAMMENFASSUNG

Einleitung und Ziele Es ist nicht bekannt, ob die Kombination von Bewegung und Supplementierung mit verzweigtkettigen Aminosäuren (BCAA) vorteilhafter war als die alleinige Verabreichung bei Sarkopenie im Zusammenhang mit Leberzirrhose (LC). Die von uns verwendeten Smartphone-Anwendungen bieten eine kontinuierliche und leicht erweiterbare Behandlung von chronischen Lebererkrankungen (CLD). Diese Studie soll die Auswirkungen von unbeaufsichtigten Gehübungen mit WeChat in Kombination mit einer BCAA-Supple-

mentierung auf die Skelettmuskelmasse und -kraft bei LC untersuchen.

Material und Methoden Die 127 LC-Patienten nach Child-Pugh A/B-Kriterien wurden der Gruppe A (BCAA-Supplemente, n = 42), der Gruppe B (Gehübung, n = 43) und der Gruppe C (Gehübungen plus BCAA-Supplemente, n = 42) zugeordnet. Labordaten, durchschnittliche Tagesschritte, Serum-BCAA, Skelettmuskelmasse-Index (SMI) und Griffkraft wurden vor und 3 Monate nach den Eingriffen analysiert.

Ergebnisse Bei den 124 Patienten, die die Interventionen durchführten, waren Albumin und tägliche Schritte in allen Gruppen signifikant erhöht (p = 0,0001). Nach der Intervention waren die BCAAs in Gruppe A (A vs. B, p = 0,001) und C (C vs. B, p = 0,012) signifikant erhöht; während die täglichen Schritte nach der Intervention in Gruppe B (B vs. A, p = 0,0001) und C (C vs. A, p = 0,0001) höher waren. Griffstärke (C vs. A, p = 0,020; C vs. B, p = 0,036) und SMI (C vs. A, p = 0,035; C vs. B, p = 0,012) waren in Gruppe C erhöht. Die Prävalenz von Sarkopenie war signifikant verringert in Gruppe C (p = 0,015).

Schlussfolgerungen Die Kombination von unbeaufsichtigten Gehübungen mit Smartphone-Anwendungen und BCAA-Supplementierung könnte eine wirksame und sichere Behandlung für Zirrhose-Patienten mit Child-Pugh A/B sein, um die Skelettmuskelmasse und -kraft zu verbessern oder das Fortschreiten der Sarkopenie zu verhindern.

Introduction

Sarcopenia, characterized by generalized loss of skeletal muscle volume and strength, is a major element of malnutrition in liver cirrhosis (LC). Sarcopenia and pre-sarcopenia were found not to be rare even in patients with chronic liver disease (CLD), including those in early stages [1]. The annual rates of skeletal muscle volume loss were 1.3 %, 3.5 %, and 6.1 % for patients with Child–Pugh class A, B, and C, respectively [2]. The importance of sarcopenia or pre-sarcopenia is that it's associated with not only reduced quality of life, but also increased decompensation event frequency and prolonged hospitalization, affecting the overall prognosis of cirrhosis [3]. For patients with cirrhosis, early diagnosis and appropriate treatment for sarcopenia are important. Although the clinical significance of sarcopenia in cirrhosis has been widely recognized, effective therapies are still to be discovered [4]. Reported strategies for treating sarcopenia related to cirrhosis include exercise regiments and supplementation with branched-chain amino acid (BCAA) [5, 6]. Previous studies have shown the superiority of exercise combined with BCAA supplementation in improving muscle mass, muscle strength, and physical function [1, 7, 8, 9]. However, most of them used pre-post-intervention study design and few emphasized comparison of interventions administrated combined or separately. Whether the combined intervention was more beneficial is still unknown.

Furthermore, traditional supervised exercise was mainly engaged in by professionals, resulting in high cost [10]. The specified repetitive content or form of supervised exercise also makes it difficult to develop an exercise habit or keep on once the intervention has stopped. As most patients in the early stage of LC don't need to be in hospital for a long time, long-term effects of interventions should be of concern. Rapidly expanding availability of smartphones provides a way to deploy interventions in a simple mode. WeChat (the Chinese version is WeiXin), like Facebook in the USA, as a representative form of modern messaging software, is widely used in China. We could easily record the routine activities such as daily steps through the "WeRun" modular. It has been demonstrated that using the WeChat application for a follow-up visit was time-effective, cost-effective, and convenient [11]. It may also help make an exercise habit in the patients' community life that would work for a long time. Nevertheless, a recent study reported high acceptance but low usage of smartphone applications for the management of cirrhosis [12].

We hypothesized that unsupervised exercise using WeChat combined with BCAA supplementation would benefit loss of muscle volume and strength in cirrhosis. The purpose of this study is to investigate the effects of walking exercise using WeChat combined with BCAA supplementation on skeletal muscle mass and muscle strength in LC patients.

Materials and Methods

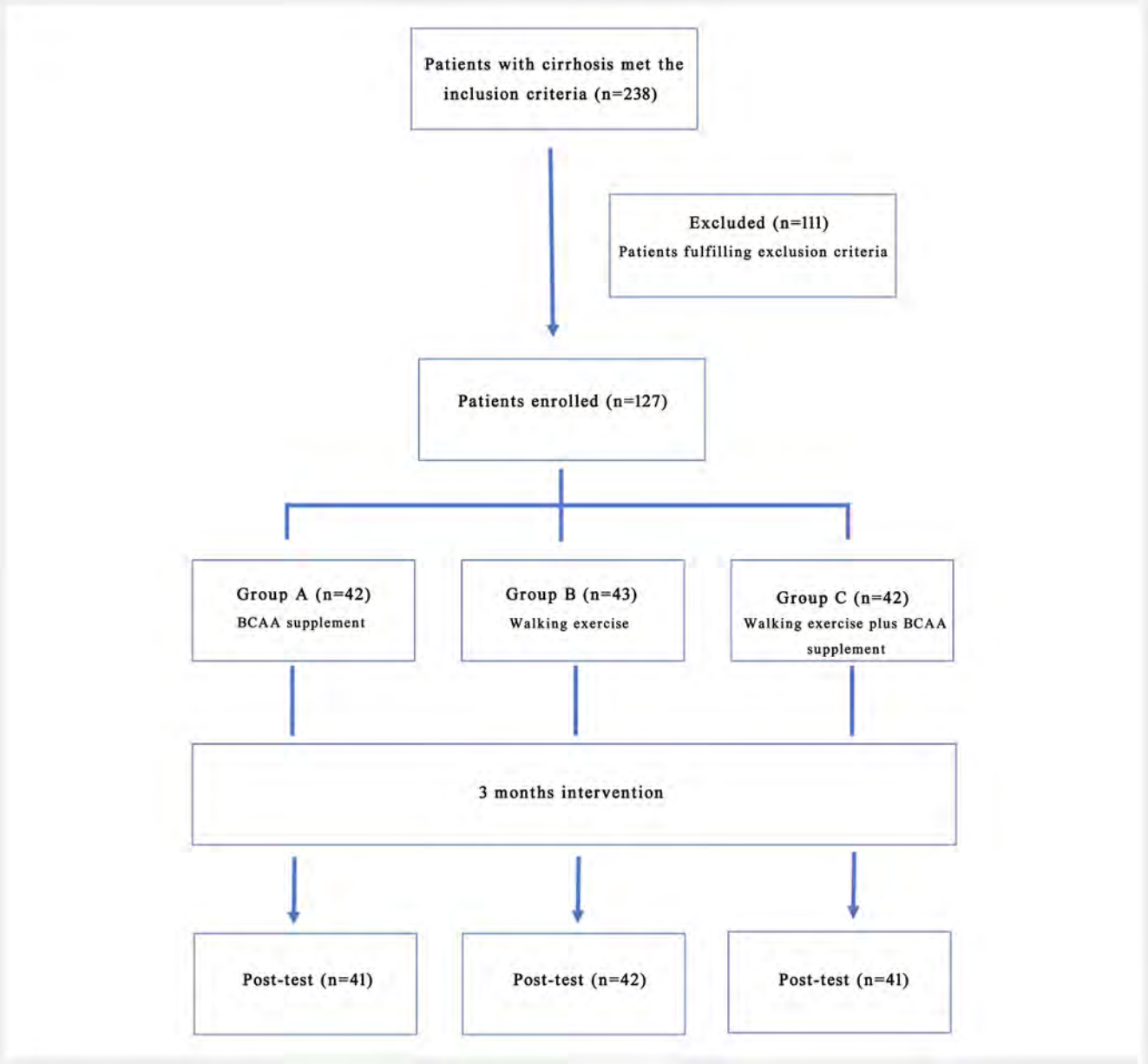
Patients

This study was an open-label prospective study. LC patients of Child–Pugh class A/B were recruited from June 2020 to May 2021 at the Sixth People's Hospital of Chengdu (Chengdu, Sichuan Province, China). Diagnosis of cirrhosis were based on the Chinese guideline for diagnosis and treatment of LC [13]. They were assigned to three groups according to the patients' personal desires: Group A, patients with oral BCAA supplements; Group B, patients with walking exercise (additional 2000 steps/day); and Group C, those who received both BCAA supplements and walking exercise. The leading inclusion criteria were as follows: 1) age ≥ 18 years, and 2) presence of cirrhosis based on medical history, physical examination, laboratory tests, or portal hypertension features from ultrasound or endoscopy. Patients of Child–Pugh C or those with refractory ascites might be difficult in dietary intake or walking. Thus, the exclusion criteria were as follows: 1) Child–Pugh class C; 2) uncontrolled ascites; 3) other disease conditions such as diabetes mellitus, coronary heart disease, pulmonary edema, or chronic kidney disease; 4) malignant tumors including hepatocellular carcinoma; 5) BCAA supplementation within 6 months before the date of entry; and 6) systemic bodybuilding within 6 months before the date of entry.

Study Protocol

Sample size for each group was calculated to be n = 29.6 with the problem probability set to 0.15 and the confidence level set to 95 % according to previous studies. Of the 238 adult patients with

LC, 111 patients were excluded, and 127 patients were included on the basis of the above criteria. The 127 participants were assigned to group A (n = 42), group B (n = 43), and group C (n = 42) after enrollment (▶ **Fig. 1**). Participants in every group underwent conventional health education and physical and laboratory examinations, which included serum BCAA, skeletal muscle mass index (SMI), and grip strength. Average daily steps were calculated via smartphone app (WeChat, Tencent Corporation, China) for 2–3 weeks. Then patients in group A received oral BCAA supplementation (CLEAR BCAA, protein 8.9 g, including L-leucine 3000 mg, L-isoleucine 750 mg, L-valine 750 mg; 159 kcal/day; Nortland Biotechnology Co. Ltd, China) as a late evening snack. Time and amount of amino acid they took every day were collected by a research assistant through the WeChat application to monitor the BCAA intake accurately. Patients in group B were prescribed walking exercise for an additional 2000 steps/day. Data of daily steps and heart rates were recorded through a smart bracelet interconnected with the WeChat application in the WeRun model, then sent manually to research assistants in the form of screenshots by the patients themselves before going to sleep every night. Research assistants would send exercise tips and answer questions from participants via WeChat message to help achieve exercise goals. Patients were informed that heart rates should not exceed 60 % of the maximum heart rate during walking. Participants in group C received both interventions for 3 months. Information security and privacy protection clauses of WeChat met the ISO/IEC 27701:2019 standard certification. Strict compliance with information security and privacy protection were taken during the whole study process.



▶ **Fig. 1** Flow chart of participant selection.

Laboratory methods

Laboratory data (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, total bilirubin, prothrombin time, BCAA) were analyzed at enrollment, as well as 1, 2, and 3 months after starting the nutrition supplementation or exercise protocol. A blood test of BCAA was accomplished by the Clinical Laboratory Center of the Sixth People's Hospital of Chengdu through the colorimetric method, the testing kit provided by Sigma-Aldrich Life Science & Tech. Co., Ltd., Wuxi, China.

Measures of SMI and grip strength

A computerized tomography scan was used to estimate skeletal muscle volume at enrollment and at the end of the intervention period. Skeletal muscle areas were calculated on axial sections at the level of the third lumbar vertebra (L3) of CT images (Philips 256 iCT), using IntelliSpace Portal software. The psoas major, erector spinae, quadratus lumborum, transversus abdominis, extra-abdominal oblique, and intra-abdominal oblique muscles were delineated by density thresholds ranging from −29 to 150 Hounsfield units. The muscle area (cm^2) at the L3 level was normalized by the square of height (m^2) to obtain SMI at L3 (L3 SMI, cm^2/m^2). Grip strength was measured at enrollment and every month during the study period using a KYTO 2324-type grip force meter. Two measurements were obtained from each hand and the average of the higher right- or left-sided values was recorded as the grip strength value.

Diagnosis of sarcopenia

According to the Chinese criteria [14], sarcopenia is defined as the presence of decreased handgrip strength (< 25 kg for men and < 18 kg for women) and decreased muscle mass (SMI < 50 cm^2/m^2 for men and < 39 cm^2/m^2 for women).

Ethical Statement

Written informed consent was obtained from each patient included in the study, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Ethics Committee of the Sixth People's Hospital of Cheng Du (APPROVAL NUMBER: 2019-S-004, 5 November 2019).

Statistical analysis

All statistical analyses were performed using the SPSSAU data scientific analysis platform (http://spssau.com/). Categorical variables were described by quantity and percentage and compared by Chi-square test. The normally distributed continuous variables are described as the means with the standard error (mean ± SEM) and compared by one-way analysis of variance (ANOVA) to determine significant differences within or between the groups. The *post hoc* Student–Newman–Keuls analyses were used when significance was found. A p value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

Conventional treatments such as liver protection, anti-virus drugs, and diuretic therapy were administrated to patients during the study period. Out of 127 enrolled participants, 124 completed the intervention, and there were 3 dropouts. Two patients were unable to tolerate a late evening snack because of the discomfort related to BCAA supplementation in the first week, one in group A and another in group C. One patient were excluded because of moving to another area in group B. None of the patients decreased food intake during dinner because of the late evening snack. There were no adverse events caused by the interventions. ▶ **Table 1** presents the baseline characteristics of group A (n = 41), group B (n = 42), and group C (n = 41). No significant differences were observed between groups.

Comparison of Muscle Mass, Muscle Strength, and Blood Indicator Variables Among Groups

Comparisons of pre- and post-intervention changes among groups in muscle mass, muscle strength, and blood indicator variables are shown in ▶ **Table 2**. Serum albumin and daily steps were significantly increased after 3-month interventions in all groups ($p = 0.0001$). In group A, remarkable post-intervention increases in BCAA ($p = 0.001$) and grip strength ($p = 0.020$) were observed. Meanwhile, in group C, post-intervention elevation of BCAA ($p = 0.005$), grip strength ($p = 0.0001$), and SMI ($p = 0.0001$) were seen. Prevalence of sarcopenia was significantly decreased in group C after intervention ($p = 0.015$). Between-group comparisons showed serum BCAA levels were significantly higher after nutrition supplementation in group A (group A vs B, $p = 0.001$) and group C (group C vs B, $p = 0.012$;). Meanwhile, daily average steps in group B (group B vs A, $p = 0.0001$) and group C (group C vs A, $p = 0.0001$), after an additional 2000 steps/day prescribed through WeChat, were more than those in group A. Post-intervention grip strength (group C vs A, $p = 0.020$; group C vs B, $p = 0.036$) and SMI (group C vs A, $p = 0.035$; group C vs B, $p = 0.012$) in group C were significantly greater than in the other two groups. No other significant differences were observed within and between groups.

Time Course of Changes in Plasma BCAA and Daily Steps

The time course of changes in serum BCAA and daily steps are shown in ▶ **Fig. 2**. The average level of BCAA in the blood was significantly increased in both group A and group C after nutrition supplementation (group A, 482.85 ± 32.81 vs 454.73 ± 40.48, $p = 0.001$; group C, 477.37 ± 30.02 vs 454.37 ± 37.24, $p = 0.005$;). Contrarily, there was no significant change between day 0 and 3 months in Group B (456.98 ± 34.02 vs 452.10 ± 42.79, $p = 0.525$). Disparity among groups appeared after the first month. Remarkably, promoted BCAA concentrations were observed in group A (group A vs B, 482.85 ± 32.81 vs 456.98 ± 34.02, $p = 0.001$) and group C (group C vs B, 477.37 ± 30.02 vs 456.98 ± 34.02, $p = 0.012$) at the end of 3 months. Significant increases in average

▶ **Table 1** Baseline characteristics of participants.

	Group A (n = 41)	Group B (n = 42)	Group C (n = 41)	p Value
Age (years)	56.29 ± 9.88	57.12 ± 7.76	55.78 ± 9.01	0.788
Gender (male/female)	27/14	31/11	23/18	0.237
Etiology (HBV/alcohol/NAFLD/others)	18/9/12/2	22/10/7/3	28/4/7/2	0.307
Child–Pugh grade (A/B)	22/19	28/14	21/20	0.309
BMI (kg/m^2)	23.09 ± 2.83	22.37 ± 2.83	22.64 ± 3.04	0.525
ALT (U/L)	85.00 ± 61.75	76.57 ± 44.89	71.71 ± 44.78	0.493
AST (U/L)	66.34 ± 43.56	56.05 ± 29.66	58.71 ± 34.72	0.413
ALP (U/L)	117.10 ± 68.73	112.79 ± 79.51	101.05 ± 48.15	0.533
Serum albumin (g/L)	32.07 ± 4.73	33.40 ± 4.73	31.97 ± 4.14	0.282
Total bilirubin (μmol/l)	38.25 ± 14.88	33.92 ± 11.04	37.80 ± 13.58	0.246
Prothrombin time (%)	62.59 ± 10.62	62.55 ± 9.95	62.32 ± 10.79	0.992
BCAA (μmol/l)	454.73 ± 40.48	452.10 ± 42.79	454.37 ± 37.24	0.949
Daily steps	5753.56 ± 907.52	5554.40 ± 746.91	5830.44 ± 839.64	0.300
Grip strength (kg)	25.73 ± 4.95	26.62 ± 6.39	24.08 ± 6.19	0.143
SMI (cm^2/m^2)	50.96 ± 8.44	49.66 ± 9.04	48.21 ± 9.06	0.375
Sarcopenia (yes/no)	11/30	12/30	14/27	0.751

Categorical variables are given as numbers. Continuous variables are given as medians and ranges in parentheses. BMI, body mass index; HBV, hepatitis B virus; NAFLD, nonalcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BCAA, branched-chain amino acid; SMI, skeletal muscle mass index.

daily steps were observed in each group since the end of month 1. Meanwhile, after an additional 2000 steps/day prescribed, the average number of daily steps were more in group B (group B vs A, 7998.38 ± 1072.02 vs 6316.85 ± 1067.32, $p = 0.0001$) and group C (group C vs A, 8292.10 ± 1042.85 vs 6316.85 ± 1067.32, $p = 0.0001$) than in group A. These results preliminarily confirmed the effect of interventions in each group.

Time Course of the Change Rates in SMI and Grip Strength

The median change rates of SMI from day 0 were 1.26 % at 3 months in group A, 2.33 % in group B, and 13.00 % in group C. A significant difference was observed among groups at 3 months ($p = 0.0001$), shown in ▶ **Fig. 3a**. The change rates of grip strength from day 0 were 6.10 % at 1 month, 8.18 % at 2 months and 10.12 % at 3 months in group A. Similarly, change rates of grip strength from day 0 were 4.53 % at 1 month, 5.72 % at 2 months, and 7.59 % at 3 months in group B. Meanwhile, in group C, change rates of grip strength from day 0 were 14.85 % at 1 month, 18.69 % at 2 months, and 23.53 % at 3 months, which were significantly greater than in any other two groups ($p = 0.0001$), as shown in ▶ **Fig. 3b**. These results demonstrated that a combination of unsupervised walking exercise and BCAA was more effective in improving skeletal muscle mass and strength than those administrated alone in patients of cirrhosis.

Prevalence of Sarcopenia in Groups

Sarcopenia were respectively diagnosed in 11 patients in group A (11/41, 26.83 %), in 12 patients in group B (12/42, 28.57 %), and in 14 patients in group C (14/41, 34.15 %) at the beginning of this study. At 3 months, 10 patients in group A and 11 patients in group B remained sarcopenic. No significant differences were observed in either group A and group B ($p = 0.500$), but in group C, 10 out of 14 patients no longer met the diagnostic criteria at 3 months. Thus, the prevalence of sarcopenia was significantly reduced to 9.76 % in group C ($p = 0.007$), as detailed in ▶ **Fig. 4**. These results suggested walking exercise plus BCAA supplementation was more useful in treating sarcopenia in LC patients with Child–Pugh A/B.

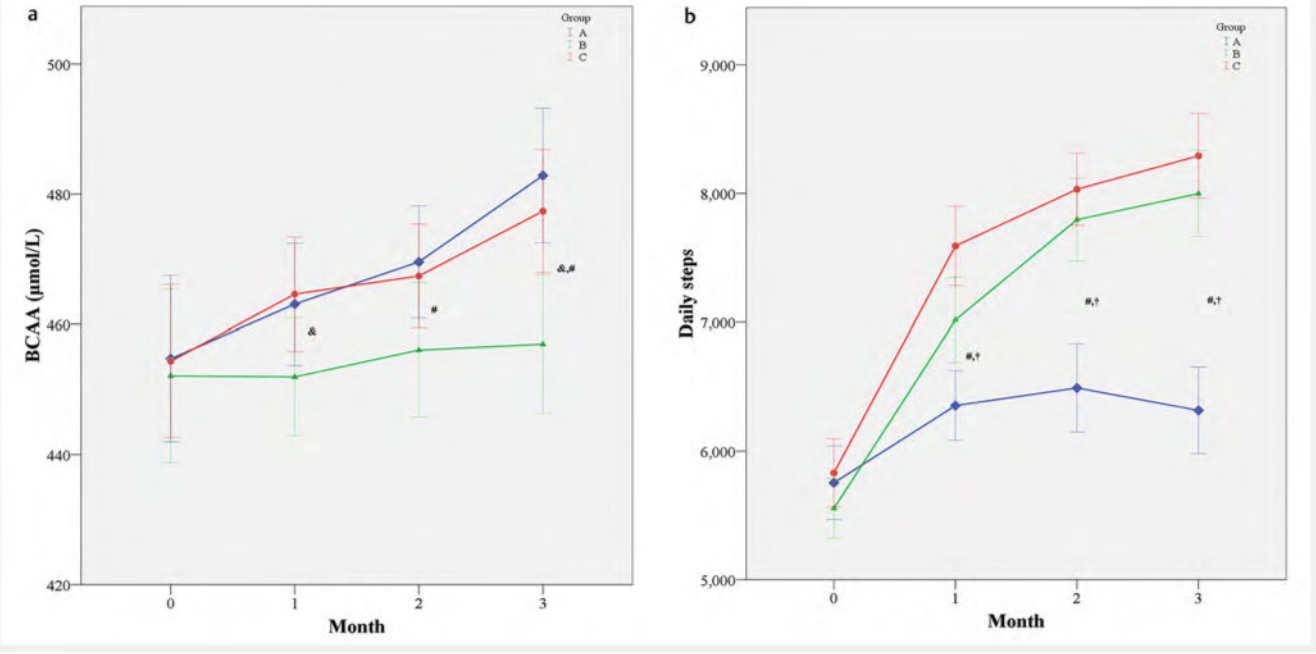
Discussion

In this study, parameters reflecting skeletal muscle mass and muscle strength were evaluated after 3 months of interventions in participants of LC. Since it's hypothesized that an earlier intervention at a time when anabolic potential exists may be more effective than an intervention at a refractory stage of muscle wasting [15], patients with Child–Pugh class A/B were enrolled. As we know, management of CLD is a long-term process and hospitalizations were not always essential in this population. Nowadays, the vast majority of people own smartphones; smartphone applications may have the chance to provide a more continuous and easily expandable

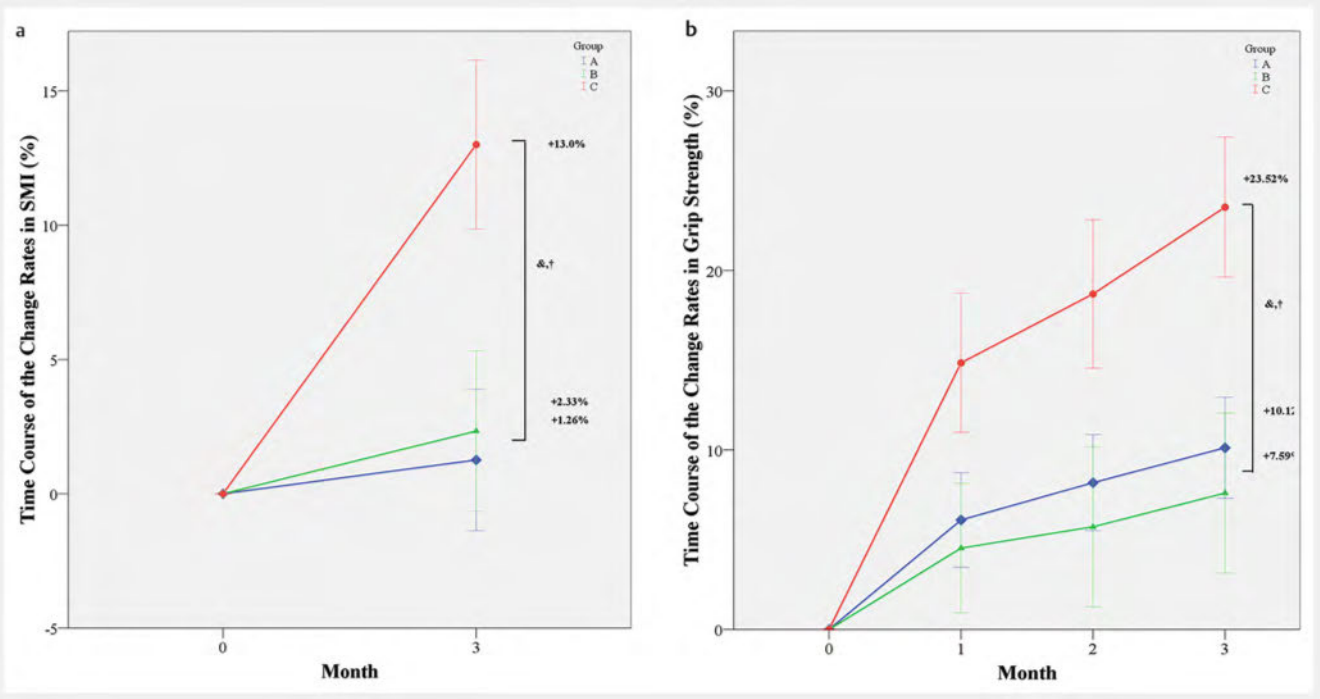
▶ **Table 2** Comparison of Muscle Mass, Muscle Strength, and Blood Indicator Variables Among Groups After 3-Month interventions.

	Group A (n = 41)		Group B (n = 42)		Group C (n = 41)		*p* Value
	Baseline	Post intervention	Baseline	Post intervention	Baseline	Post intervention	
BMI (kg/m^2)	23.09 ± 2.83	23.25 ± 1.99	22.37 ± 2.83	22.51 ± 2.38	22.64 ± 3.04	23.20 ± 2.94	0.533
ALT (U/L)	85.00 ± 61.75	75.34 ± 43.69	76.57 ± 44.89	63.60 ± 34.69	71.71 ± 44.78	62.12 ± 33.30	0.186
AST (U/L)	66.34 ± 43.56	70.29 ± 42.12	56.05 ± 29.66	65.38 ± 33.58	58.71 ± 34.72	72.29 ± 31.84	0.274
ALP (U/L)	117.10 ± 68.73	104.32 ± 50.20	112.79 ± 79.51	112.24 ± 49.56	101.05 ± 48.15	110.22 ± 46.90	0.836
Serum albumin (g/L)	32.07 ± 4.73	35.47 ± 3.26*	33.40 ± 4.73	36.12 ± 3.70*	31.97 ± 4.14	35.37 ± 3.56*	0.0001
Total bilirubin (μmol/l)	38.25 ± 14.88	37.06 ± 11.37	33.92 ± 11.04	36.39 ± 11.68	37.80 ± 13.58	37.98 ± 11.48	0.622
Prothrombin time (%)	62.59 ± 10.62	59.22 ± 9.34	62.55 ± 9.95	60.83 ± 8.39	62.32 ± 10.79	61.95 ± 8.61	0.570
BCAA (μmol/l)	454.73 ± 40.48	482.85 ± 32.81*b	452.10 ± 42.79	456.98 ± 34.02	454.37 ± 37.24	477.37 ± 30.02*b	0.0001
Daily steps	5753.56 ± 907.52	6316.85 ± 1067.32*	5554.40 ± 746.91	7998.38 ± 1072.02*a	5830.44 ± 839.64	8292.10 ± 1042.85*a	0.0001
Grip strength (kg)	25.73 ± 4.95	28.53 ± 4.09*	26.62 ± 6.39	28.81 ± 5.52	24.08 ± 6.19	31.32 ± 4.94*ab	0.0001
SMI (cm^2/m^2)	50.96 ± 8.44	51.49 ± 6.92	49.66 ± 9.04	50.76 ± 7.28	48.21 ± 9.06	55.22 ± 6.74*ab	0.004
Sarcopenia (%)	26.83	24.39	28.57	26.19	34.15	9.76*	—

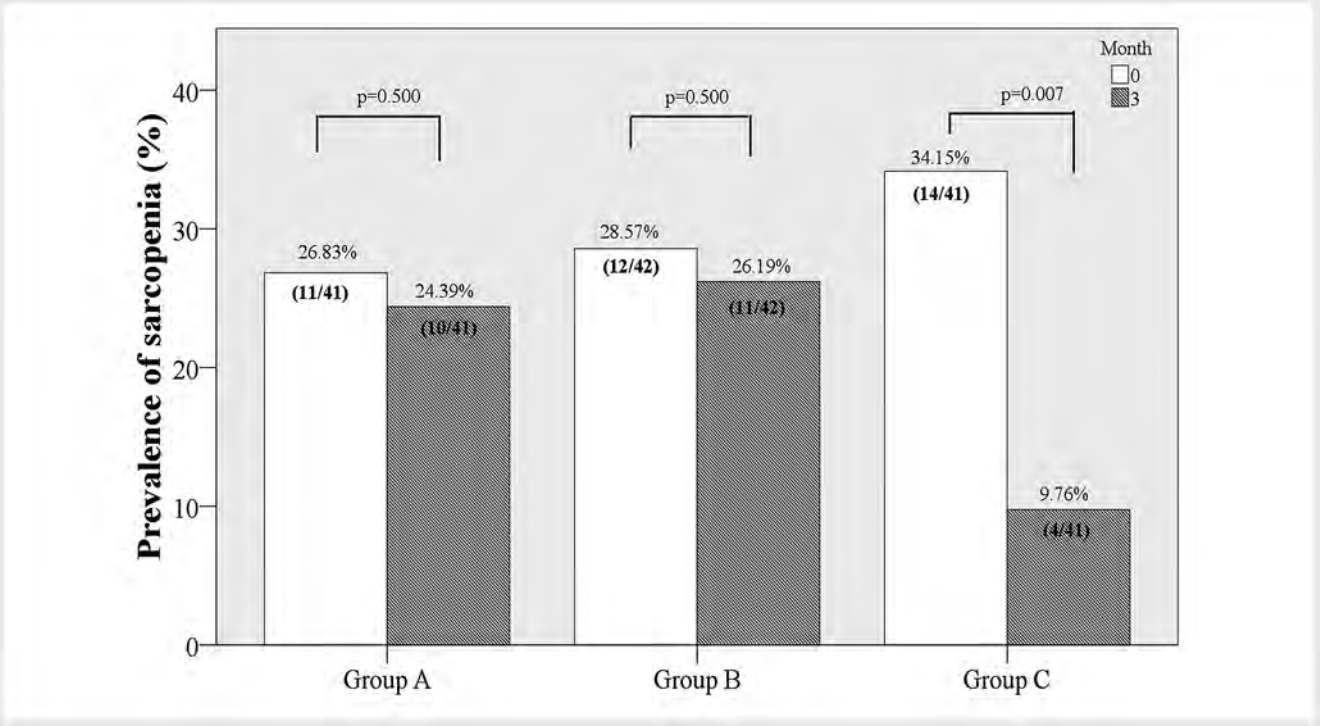
*$p < 0.05$ vs baseline; [a] $p < 0.05$ vs group A; [b] $p < 0.05$ vs group B; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BCAA, branched-chain amino acid; SMI, skeletal muscle mass index.



▶ **Fig. 2** Time course of changes in plasma BCAA **a** and daily steps **b**. Group A vs B, #p < 0.05; Group B vs C, &p < 0.05; Group A vs C, †p < 0.05; BCAA, branched-chain amino acid.



▶ **Fig. 3** Time course of the change rates in SMI **a** and grip strength among groups **b**. Group A vs B, #p < 0.05; Group A vs C, †p < 0.05; SMI, skeletal muscle mass index.



▶ **Fig. 4** Prevalence of sarcopenia at day 0 and 3 months in groups.

method of outpatient disease monitoring. However, data about the use of these communication tools in cirrhosis with sarcopenia and pre-sarcopenia are still insufficient. To the best of our knowledge, we first conducted this prospective controlled study to demonstrate that an unsupervised walking exercise using WeChat combined with BCAA supplementation benefits muscle conditions and prevents progress of sarcopenia in LC adults.

Onset and progression of sarcopenia include malabsorption, dysregulated metabolism, reduced nutritional intake, hormonal alterations, increased loss of muscle, and hyperammonemia [16]. Cirrhosis is a state of accelerated starvation caused by abnormal liver function. Within 10 h of fasting in patients with cirrhosis, fatty acid oxidation, muscle, and hepatic glycogen reduction are equivalent to what would be observed in healthy subjects after 3 days of starvation [17]. Low glycogen stores increase the need for gluconeogenesis, resulting in impaired muscle biosynthesis and increased muscle proteolysis. Nevertheless, nutritional and metabolic alterations do not explain all of the low muscle mass in cirrhosis. The exact mechanism contributing to muscle atrophy in cirrhosis has not been clearly identified. Nutritional therapy, especially BCAA supplementation, has shown significant benefit, while studies on exercise have been controversial [18]. Applying acute exercise to cirrhosis individuals might be challenging because of stimulating oxidative stress and proinflammatory cytokines synthesis, which in turn lead to liver damage, portal hypertension, and development of complications [19]. Meanwhile, infrequent physical activity with low intensity might be more useful with no decompensation events associated with exercise [9]. As mentioned above, high acceptance but low usage of smartphone applications was reported for the management of cirrhosis [12]. We believe that setting an achievable goal is important, considering the lower level of daily activity in cirrhosis individuals than in the general republic. Therefore, an additional 2000 steps/day were prescribed through the WeChat application in the form of unsupervised walking in the current study. As displayed in ▶ **Fig. 2**, average daily steps began to increase from the end of month 1, until there were far more than 2000 steps over the intervention period in patients administered walking exercise. A similar trend was observed in patients who received BCAA treatment alone, but a rising number of daily steps remains remarkably higher in group B and group C after 3 months. This could be attributed to goal setting and maintenance of exercise habits in patients conducting walking exercises. Besides, walking activity using WeChat indicates good compliance and safety through unsupervised exercise. No participants dropped out owing to adverse events associated with exercise, no significant changes in laboratory data were seen except an ascent of albumin in research. The advising of unsupervised physical activity of low to medium intensity through the smartphone application seems to be workable and helpful in forming an exercise habit in LC patients of Child–Pugh A/B. However, no benefits in skeletal muscle mass and prevalence of sarcopenia were established in participants undertaking exercise alone, even in grip strength. We think this may be due to the low intensity of walking and no resistance training being provided [20]. Of course, unchanged grip strength could also be explained by the lower limb muscles being affected during walking but not the wrist muscles. Interestingly, the combination of walking exercise and BCAA supplementation results in a different effect. Post-intervention SMI and grip strength were significantly improved, as well as when compared between groups of these provided alone. The prevalence of sarcopenia also declined in group C. There is strong evidence BCAA plays an important role in the formation and maintenance of the skeletal muscle [21]. BCAAs, particularly leucine, activate the mammalian target of rapamycin (mTOR) signaling, stimulating the synthesis of glycogen and proteins [22]. Moreover, BCAA plays a compensatory role in ammonia detoxification and clearance in cirrhosis [23, 24, 25]. Accumulation of ammonia in muscle results in mitochondrial dysfunction, which in turn causes muscle oxidative damage, further exacerbating sarcopenia [26]. It was reported that chronic liver disease has a low serum level of BCAA [27]. Concentrations of BCAA were significantly related to muscle mass and muscle strength in cirrhosis, even in those not receiving BCAA supplementation [1]. A recent meta-analysis suggested BCAA improves SMI and mid-arm muscle circumference in sarcopenia with cirrhosis [4]. We similarly noted the efficiency of oral BCAA supplementation. As revealed in our study, serum BCAA, albumin, daily steps, grip strength, and SMI were elevated in group A after 3 months of oral supplementation, though not statistically in SMI. The insignificant changes in SMI could be partially explained by the short intervention duration compared with previous literature. We also suggested the coordinated action of walking exercise and BCAA supplementation in ameliorating sarcopenia. Several pre-post-interventional designed studies [1, 7, 8] have shown the superiority of BCAA combined with exercise. In a randomized trial [9], lower thigh circumference and the 6 min walking test were significantly improved in cirrhosis patients (n = 8) with combined interventions, compared with patients (n = 9) with no intervention. In a study of elderly women with sarcopenia [28], muscle volume and function showed greater improvements with both BCAA supplementation and exercise for 3 months than with only BCAA supplementation. In the present study, we emphasized a comparison between different interventions and found that exercise plus BCAA supplementation might be more superior in improving SMI, grip strength, and sarcopenia than those given alone in relatively early cirrhosis, or at least the effect of nutrition supplementation was moved up according to the time course of the change rates in SMI and grip strength (▶ **Fig. 2**) in consideration of previous studies [1, 7, 8]. Aerobic exercise, such as walking, was found to contribute to the inductions of mitochondrial biogenesis and dynamics and mitochondrial metabolism restoration, as well as to decrease the catabolic genes expression and increases muscle protein synthesis [29]. Exercise upregulates insulin-like growth factor 1 (IGF-1), which brings downregulation of myostatin, resulting in improvement of insulin sensitivity and an increase in muscle protein synthesis [30]. However, production of ammonia elevates at the same time [31]. After exercise, BCAAs help to increase muscle mass and improve insulin resistance and glucose uptake in the muscles [32]. Meanwhile, BCAAs may work as substrates in ammonia metabolism in skeletal muscles, as mentioned above [25].

Compared with previous trials, WeChat, a smartphone application, was used to guide the urban-life-based exercise of cirrhosis patients in this study. There were several advantages. First, WeChat has been widely used in China. The application would remind patients to exercise and record steps automatically. WeChat would save the time of patients who no longer need to come back to hospital for guided training. In addition, patients and research assistants could communicate with each other once needed. It has little impact on patients' normal lives and is relatively safer than patients doing exercise alone. Finally, WeChat is free,

and it is cost effective for the management of chronic diseases such as liver cirrhosis.

There are some limitations in this study. First, this study was not a randomized control trial, and no placebo group was set because the ethics committee insisted that all patients should have the right to select their disease management mode, and all patients should be provided appropriate interventions. Second, the period of the study was short, and we are unable to investigate changes of SMI every month, for we used radiological examination to calculate SMI. Furthermore, we didn't include data of blood ammonia and health-related quality of life. That will be our next exploration approach. Nevertheless, our findings indicated the effectiveness and feasibility of a combination of unsupervised walking using a smartphone and BCAA supplementation for ameliorating skeletal muscle mass and strength in Child–Pugh class A/B cirrhosis patients.

Conclusion

In conclusion, the present study suggests that the combination of unsupervised walking exercise using smartphone applications and BCAA supplementation might be an effective and safe treatment option for cirrhosis patients with Child–Pugh class A/B to improve skeletal muscle mass and strength or prevent progress of sarcopenia.

Data availability statement

Supplementary material associated with this article can be found, in the online version, at http://www.chictr.org.cn/showproj.aspx?proj = 55293.

Clinical trial results

Trial registration: 06–27–2020; registration number: ChiCTR2000034175. Posting in registry of results of the same or closely related work: none.

Contributors' Statement

Authors' contributions are as follows. Study conception and design: Qian Xiang, Jing Xiong, Xia Chen, and Zhijing Zhao. Acquisition of data: Qian Xiang, Jing Xiong, Zhijing Zhao, and Ying Liao. Sample management and processing: Qian Xiang, Ting Zhou, and Ying Liao. Statistical analyses: Jun Wu, Ting Zhou, Jing Xiong, and Qian Xiang. Interpretation of data: Qian Xiang, Zhijing Zhao, Jing Xiong, Ting Zhou, and Xia Chen. Drafting of the manuscript: Qian Xiang, Jing Xiong, and Zhijing Zhao. Critical revision of the manuscript for important intellectual content: Qian Xiang and Jing Xiong. Obtained funding: Qian Xiang. Administrative support: Xia Chen. Review and approval of the paper: all authors.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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