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ORIGINAL ARTICLE——LIVER, PANCREAS, AND BILIARY TRACT

Resistance exercise in combination with aerobic exercise reduces the incidence of serious events in patients with liver cirrhosis: a meta-analysis of randomized controlled trials

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Abstract

Background Exercise, particularly resistance exercise, is beneficial for sarcopenia in patients with liver cirrhosis. However, the effects of exercise on events remain unclear. We aimed to examine the effects of exercise on serious events in patients with liver cirrhosis using a meta-analysis of randomized controlled trials (RCTs).

Methods A literature search was conducted in 2022. Eleven RCTs were selected for the meta-analysis (exercise group, $n = 232$; control group, $n = 193$). Serious events were defined as death or serious complications according to the original articles. A meta-analysis was performed using a random-effects model. The primary outcome was the incidence of serious events.

Results In the 11 RCTs, the incidence of serious events was 5.6% (13/232) and 12.3% (24/193) in the exercise and control groups, respectively. However, a meta-analysis demonstrated no significant difference in the incidence of serious events between the two groups (risk difference [RD] − 0.03, 95% confidence intervals (CI) − 0.07 to 0.02). In a stratification analysis based on a combination of aerobic and resistance exercise, five RCTs ($n = 185$) were enrolled. The incidence of serious events was 6.25% (7/112) and 24.7% (18/73) in the combination exercise and control groups, respectively. A meta-analysis demonstrated a significant reduction in the incidence of serious events in the combination exercise group compared with the control group (RD − 0.12; 95% CI − 0.21 to − 0.03).

Conclusions Resistance exercise in combination with aerobic exercise reduces serious events in patients with liver cirrhosis. A combination of aerobic and resistance exercise may be beneficial to improve the prognosis of patients with liver cirrhosis.

Keywords Liver cirrhosis · Physical function · Rehabilitation · Resistance training · Serious adverse events

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Introduction

Sarcopenia and frailty are highly prevalent in patients with liver cirrhosis [1–4]. Sarcopenia and frailty are associated with an increased risk of serious events, including hepatic encephalopathy, liver failure, hepatocellular carcinoma, and infection [1–4]. A recent meta-analysis further demonstrated that sarcopenia is independently associated with a higher risk of mortality in patients with liver cirrhosis [5]. Moreover, accumulating evidence suggests that the 6-min walking distance (6MWD), a frailty index that measures the distance covered over a period of 6 min, is an independent prognostic factor in patients with liver cirrhosis [6–8]. Thus, several major clinical practice guidelines have focused on sarcopenia and frailty as important factors in the management of patients with liver cirrhosis [1–4, 9]. In particular, sarcopenia is proposed as an initial assessment item for the management of patients with liver cirrhosis in the Evidence-Based Clinical Practice Guidelines for Liver Cirrhosis 2020 [1, 2] and the usefulness of the guideline has been validated [10].

Exercise is fundamental for the prevention and improvement of sarcopenia and frailty in patients with liver cirrhosis [11]. Exercise improves aerobic endurance, muscle mass, and strength in patients with liver cirrhosis [12–15]. Exercise has also been reported to improve health-related quality of life, such as fatigue [12]. Resistance exercise, in particular, has a prominent effect on sarcopenia [12]. Resistance exercise reportedly increases muscle strength and size and has beneficial effects on general performance measures in patients with liver cirrhosis [13, 14, 16, 17].

Generally, the beneficial effects of exercise on sarcopenia have been established; however, opposing results have been reported regarding the effects of exercise on serious events in patients with liver cirrhosis. A previous study reported that exercise increases portal pressure and the risk of variceal bleeding in patients with liver cirrhosis [18]. Another study demonstrated that exercise causes marked impairment of renal function in patients with ascites [19]. These previous studies have highlighted the potential risks of exercise for serious events and subsequent poor prognosis. In contrast, several studies have reported that the incidence of serious events was equal between the exercise and control groups [12, 14, 15, 20, 21]. Moreover, a few studies demonstrated the beneficial effects of exercise on prognostic factors, including nutritional status, hepatic venous pressure gradient, and insulin resistance [21, 22]. Thus, the effect of exercise on serious events remains controversial, and no meta-analysis has addressed this clinical question.

This study aimed to investigate the effects of exercise, particularly resistance exercise, on the incidence of serious events in patients with liver cirrhosis through a meta-analysis of randomized controlled trials (RCTs).

Methods

Study design

This was a systematic review and meta-analysis of RCTs. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement [23].

Data sources

Published literature up to January 30, 2022, was searched using PubMed, Ovid MEDLINE, Scopus, and Cochrane Library literature databases.

Search terms

Potential articles were identified by search terms and Medical Subject Headings terms relevant to "exercise" OR "training" OR "physical activity"; "liver cirrhosis" OR "cirrhosis" OR "hepatic cirrhosis." Database searches were organized according to the PICOS model (Population, Intervention, Control, Outcome, Study design) [24].

Six investigators (T.K., S.K., K.H., M.T., J.T., and H.N.) independently reviewed the titles and abstracts of the identified studies. References in each report that met the selection criteria were manually searched to identify other potentially relevant studies. All relevant abstracts and full-text peer-reviewed articles published in English were analyzed.

Inclusion and exclusion criteria

Studies were selected if they met the following inclusion criteria: (1) RCT design; (2) evaluated the effects of aerobic exercise, resistance exercise, or a combination of aerobic and resistance exercises on any outcome in patients with liver cirrhosis; and (3) included information on events, including death and serious complications, during the study period. Studies were excluded if they (1) were not RCTs (non-randomized controlled clinical trials, before-and-after clinical trials, or observational cohort studies); (2) were not original research (systematic reviews, narrative reviews, commentaries, or editorials), were case reports or conference abstracts; (3) included no information about events; (5) were animal studies; or (6) were not published in English.

Primary and secondary outcomes

The primary outcome was the incidence of serious events, defined as death or any serious complications, including hepatic failure, ascites, infection, fracture, hepatocellular carcinoma, and extrahepatic cancer according to original articles reported. We also assessed the following variables as secondary outcomes: incidence of non-serious events, changes in Child–Pugh score, the model for end-stage liver disease (MELD) score, chronic liver disease questionnaire (CLDQ) [20], 6MWD, peak O_2 uptake, and maximum heart rate.

Data extraction

Ten investigators (T.K., R.H., D.N., T.T., M.K., S.K., K.H., M.T., J.T., and H.N.) individually screened the records and extracted the data. We extracted the following data from each study: first author's name, publication year, study design, number of subjects, age, sex, sample size, type of exercise (aerobic exercise/ combination of aerobic and resistance exercises), and exercise intervention (exercise time per session, frequency, and period). We also collected data on the incidence of serious events, including death and any serious events; the incidence of non-serious events; and the mean and standard deviation (SD) of the following outcomes at the baseline and end of the study: Child–Pugh score, MELD score, CLDQ, 6MWD, peak O_2 uptake, and maximum heart rate.

Quality assessment of the included studies

Two investigators (T.K. and A.K.) independently assessed the quality of the included studies. Randomized controlled trials were assessed using the criteria formulated by the Cochrane Effective Practice and Organization of Care group [25].

Data synthesis

The mean and standard deviation of the net changes in Child–Pugh score, MELD score, CLDQ, 6MWD, peak O_2 uptake, and maximum heart rate were calculated for each study. When the outcomes were reported as quartile measures, the mean and SD were calculated from the quartiles using the formula described by Wan et al. [26]. For the SD of the change from baseline to end point, we used the correlation coefficient $r = 0.7$ as a conservative estimate, as previously described [27].

Statistical analysis

All statistical analyses were performed by biostatisticians (A.K., M.K., K.E., and S.I.). We used risk differences as a summary statistic for the incidence of serious and non-serious events. The standard mean difference (SMD) and 95% confidence intervals (CI) were used as summary statistics for changes in the Child–Pugh score, MELD score, CLDQ, 6MWD, peak O_2 uptake, and maximum heart rate [28].

A meta-analysis was performed using the Review Manager Software (Review Manager 5.3; Cochrane Collaboration, Oxford, UK). A random-effects model was applied when the heterogeneity test was $P < 0.10$. Heterogeneity between studies was evaluated using Cochran's Q test, I^2 index, and t^2 test. Publication bias was assessed using the visual assessment of funnel plots, Begg's test, and Egger's regression asymmetry test. Statistical significance was set at $P < 0.05$.

Results

Search results

We identified 3004 articles using the pre-specified search criteria. Six additional reports were identified in the references (Fig. 1). After removing duplicates ($n = 1154$), 1856 articles were screened. We removed 1842 articles for the following reasons: studies unrelated to cirrhosis ($n = 213$), review articles ($n = 195$), non-RCTs ($n = 144$), editorials or letters ($n = 73$), and unrelated research ($n = 1217$). The remaining 11 studies were included in the meta-analysis (Analysis 1).

To investigate the impact of a combination of aerobic and resistance exercise on serious and non-serious events, we excluded studies on aerobic exercise alone ($n = 5$) and self-managed training ($n = 1$) from the 11 articles. The remaining 5 studies that used resistance exercise were included in the meta-analysis (Analysis 2).

Characteristics of included studies for meta-analysis

All the included studies were RCTs conducted between 2013 and 2020 (Table 1). A total of 425 patients with liver cirrhosis were included; 232 and 193 patients were classified into the exercise and control groups, respectively. The mean age of the participants in the exercise group ranged from 41.6 to 68.0 years. The study durations ranged from 4 to 27 weeks. The types of exercise included aerobic exercise ($n = 5$), a combination of aerobic and resistance exercises ($n = 5$), and self-managed training ($n = 1$).

Quality assessment

The quality of the included studies is summarized in Supplementary Table 1. All studies had a low risk of random sequence generation (Supplementary Table 1). As patients in the exercise group could not be blinded, the quality of blinding of participants and researchers, and the blinding of outcome assessments were at moderate risk. All studies had a low risk of incomplete outcome data and selective reporting.

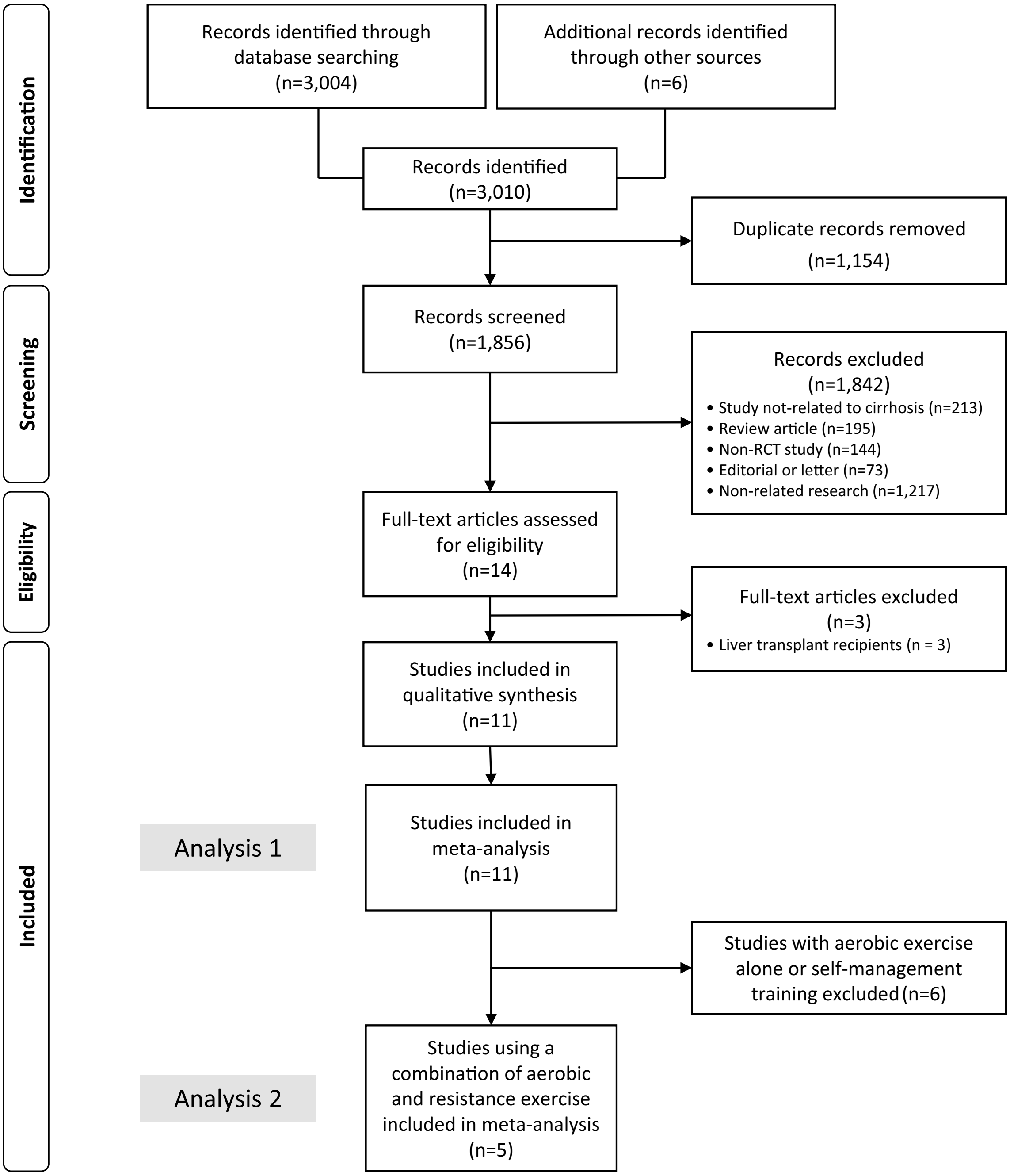


Fig. 1 Flow diagram of studies included in the meta-analysis

Heterogeneity among the studies and power analysis for meta-analysis

The I^2 and t^2 statistics did not show heterogeneity among the studies in the analysis of the incidence of serious events (Figs. 2A, 5A), incidence of non-serious events (Figs. 2B, 5B), changes in Child–Pugh score (Fig. 3A), MELD score (Fig. 3B), CLDQ (Fig. 3C), 6MWD (Fig. 4A), and peak O_2 uptake (Fig. 4B). Heterogeneity among the studies was observed only in the analysis of the maximum heart rate (Fig. 4C).

Publication bias

Publication bias was examined using funnel plots (Supplementary Figs. 1A–H, Fig. 2A, B). In Analysis 1, Begg's test showed no publication bias for the incidence of serious events (Supplementary Fig. 1A). Publication bias

Table 1 Characteristics of included studies

Author	Year	Study design	Randomized number (analyzed number)	Subjects	Mean age (years)	Sex (female/male)	Type of exercise	Exercise intervention
Kaibori et al. [22]	2013	Randomized controlled trial	51 (51)	Liver cirrhosis (Child–Pugh class A or B)	Exercise 68.0 Control 71.3	Exercise 8/17 Control 7/19	Aerobic exercise	5 min of stretching exercises, 30 min of walking at an intensity based on the anaerobic threshold of each patient, 20 min of targeted stretching exercises, and 5 min of cooling down with stretching 60 min/session, 3 times/week for 27 weeks
Román et al. [15]	2014	Randomized controlled trial	20 (17)	Liver cirrhosis (Child–Pugh class A or B)	Exercise 65.5 Control 61.0	Exercise 3/5 Control 2/7	Aerobic exercise	Treadmill walking and cycle ergometry 1 h/session, 3 times/week for 12 weeks
Zenith et al. [12]	2014	Randomized controlled trial	20 (19)	Liver cirrhosis (Child–Pugh class A or B)	Exercise 56.4 Control 58.6	Exercise 2/7 Control 2/8	Aerobic exercise	Cycle ergometer Heart rate at 60–80% of baseline peak VO_2 40–60 min/session, 3 times/week for 8 weeks
Román et al. [13]	2016	Randomized controlled trial	25 (23)	Liver cirrhosis (all patients had previous decompensation)	Exercise 62.0 Control 63.1	Exercise 4/10 Control 2/7	Aerobic exercise + Resistance exercise	Steps (final total daily step goals of over 5,000–7000/day) Resistance training 1 h/session, 3 times/week for 12 weeks
Macías-Rodríguez et al. [21]	2016	Randomized controlled trial	29 (25)	Liver cirrhosis (Child–Pugh class A or B)	Exercise 53.0 Control 51.0	Exercise 4/9 Control 2/10	Aerobic exercise	Cycle ergometer at 60–80% of the maximal theoretical age-adjusted heart rate 40 min/session, 3 times/week for 14 weeks
Mansouri et al. [39]	2017	Randomized controlled trial	80 (74)	Liver cirrhosis	Exercise 41.6 Control 41.3	Exercise 14/26 Control 12/28	Self-managed training	Self-managed training 90 min/session, 2 times/week for 4 weeks

Table 1 (continued)

Author	Year	Study design	Randomized number (analyzed number)	Subjects	Mean age (years)	Sex (female/male)	Type of exercise	Exercise intervention
Kruger et al. [40]	2018	Randomized controlled trial	40 (37)	Liver cirrhosis (Child–Pugh class A or B)	Exercise 53.0 Control 56.4	Exercise 10/10 Control 7/13	Aerobic exercise	Moderate to high-intensity cycling exercise 40–70 min/session, 3 times/week for 8 weeks
Wallen et al. [29]	2019	Randomized controlled trial	21 (8)	Liver cirrhosis (62% were Child–Pugh B/C)	Exercise + Control 49.0	Exercise + Control 4/17	Aerobic exercise + resistance exercise	Aerobic exercise (stationary cycling or walking). Circuit-based resistance exercise using body weight or portable equipment (i.e., resistance bands) 3 times/week for 8 weeks
Aamann et al. [14]	2020	Randomized controlled trial	39 (34)	Liver cirrhosis (Child–Pugh class A or B)	Exercise 61.7 Control 63.7	Exercise 4/16 Control 5/14	Aerobic exercise + Resistance exercise	Warming up using rowing machine (5 min) and progressive resistance training 1 h/session, 3 times/week for 12 weeks
Chen et al. [17]	2020	Randomized controlled trial	17 (11)	Liver cirrhosis (MELD score > 10)	Exercise 55.0 Control 54.0	Exercise 4/5 Control 2/6	Aerobic exercise + resistance exercise	Both aerobic and resistance exercising, along with multiple examples for practice 30 min/session, 5 times/week for 12 weeks
Lai et al. [20]	2021	Randomized controlled trial	83 (83)	Liver cirrhosis (54% were Child–Pugh B/C)	Exercise 62.0 Control 61.0	Exercise 29/29 Control 7/18	Aerobic exercise + resistance exercise	Resistance bands + walking 30 min/session, 3 times/week for 12 weeks

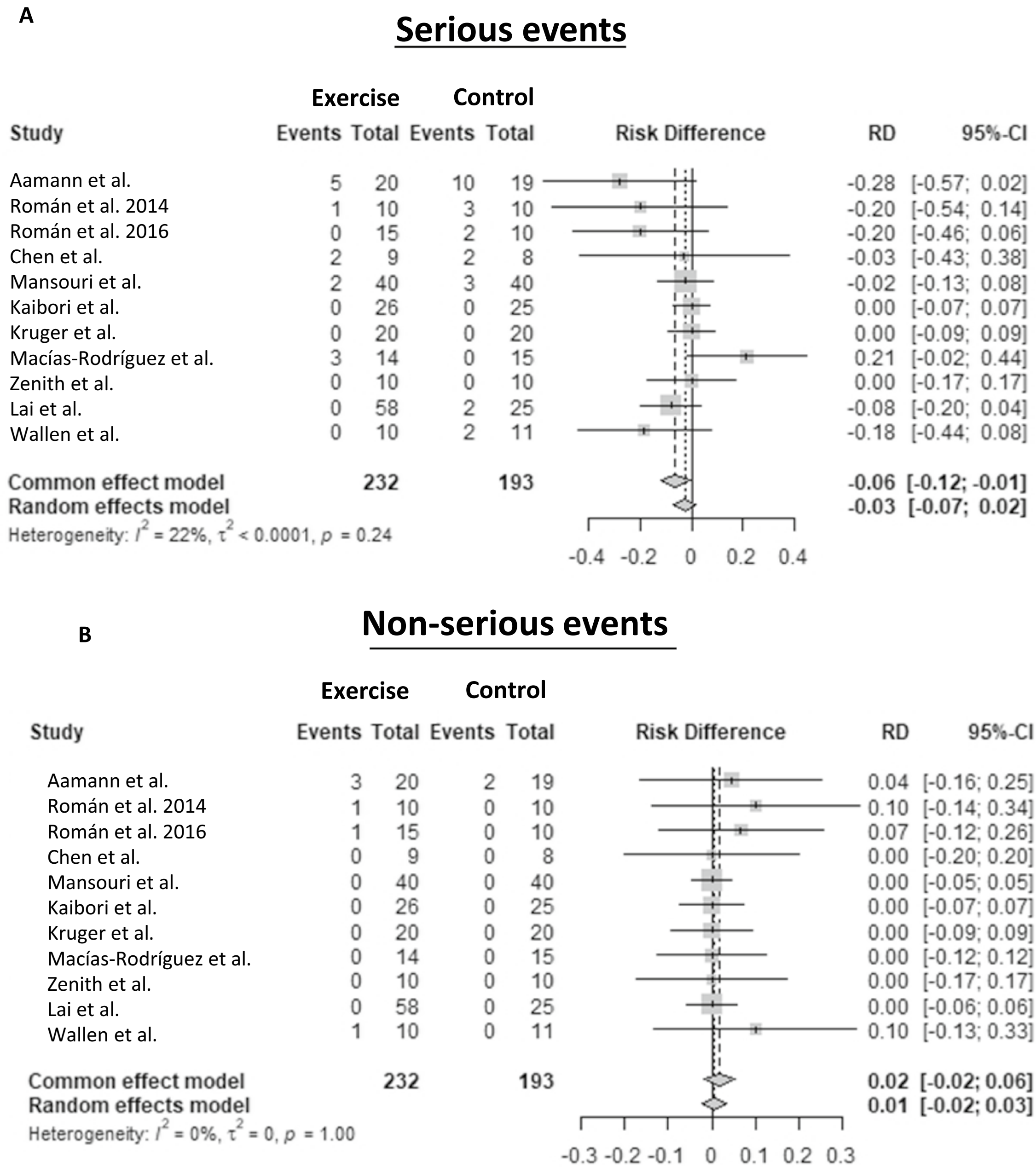


Fig. 2 Forest plot for the effect of exercise on outcomes in patients with liver cirrhosis. Incidence of **A** serious and **B** non-serious events. *RD* risk differences, *CI* confidence intervals

was observed for the incidence of non-serious events and maximum heart rate (Supplementary Fig. 1B and H). However, no publication bias was observed in the changes in Child–Pugh score, MELD score, CLDQ, 6MWD, or peak O_2 uptake (Supplementary Figs. 1A–G).

In the Egger's regression asymmetry test, there was no publication bias for the incidence of serious events, Child–Pugh score, MELD score, CLDQ, 6MWD, peak O_2 uptake, or maximum heart rate (Supplementary Figs. 1A, C–H). Publication bias was observed only for the incidence of non-serious events (Supplementary Fig. 1B).

In Analysis 2, Begg's test showed no publication bias for the incidence of serious or non-serious events (Supplementary Figs. 2A, B). In Egger's regression asymmetry test, no publication bias was observed for the incidence of serious or non-serious events (Supplementary Figs. 2A, B).

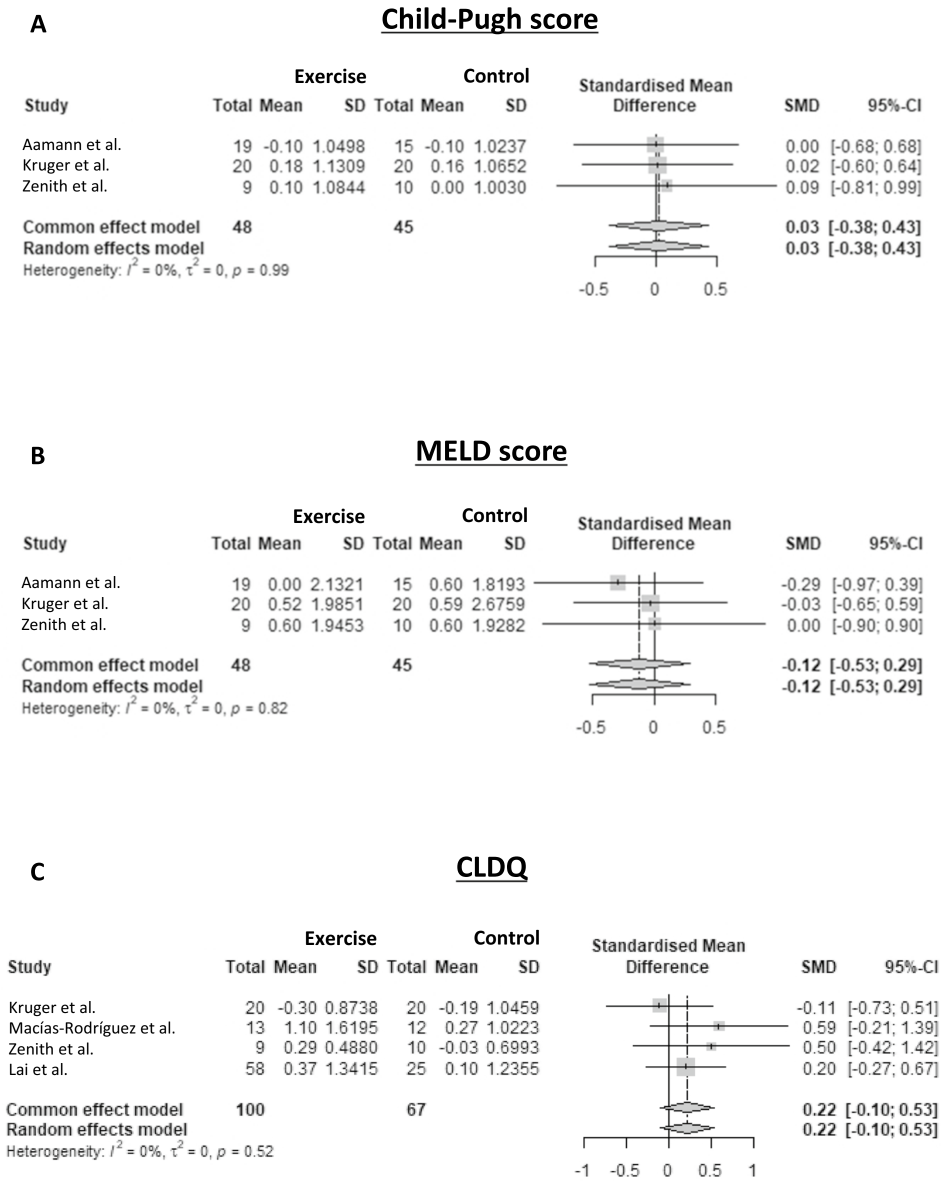


Fig. 3 Forest plot for the effect of exercise on outcomes in patients with liver cirrhosis. **A** Child–Pugh score, **B** MELD score, and **C** CLDQ. *SMD* standard mean difference, *CI* confidence intervals, *MELD* the model for end-stage liver disease, *CLDQ* chronic liver disease questionnaire

Analysis 1: meta-analysis of the effect of exercise on outcomes in patients with liver cirrhosis

Serious events

In all 11 analyzed studies, no falls or bone fractures were observed in the exercise group, whereas one patient in the control group fractured a bone in the foot (Table 2). Moreover, no patients died in the exercise group, whereas four patients died in the control group (Table 2).

The incidence of serious events was 5.6% (13/232) and 12.3% (24/193) in the exercise and control groups, respectively (Fig. 2A). The exercise group showed an approximately 7% lower incidence of serious events. However, no significant difference was observed in the incidence of serious events between the exercise and control groups (Fig. 2A).

Non-serious events

The incidence of non-serious events was 2.6% (6/232) and 1.0% (2/193) in the exercise and control groups, respectively. There was no significant difference in the incidence of nonserious events between the exercise and control groups (Fig. 2B).

Child–Pugh and MELD scores

No significant difference was observed in the changes in Child–Pugh and MELD scores between the exercise and control groups (Figs. 3A, B).

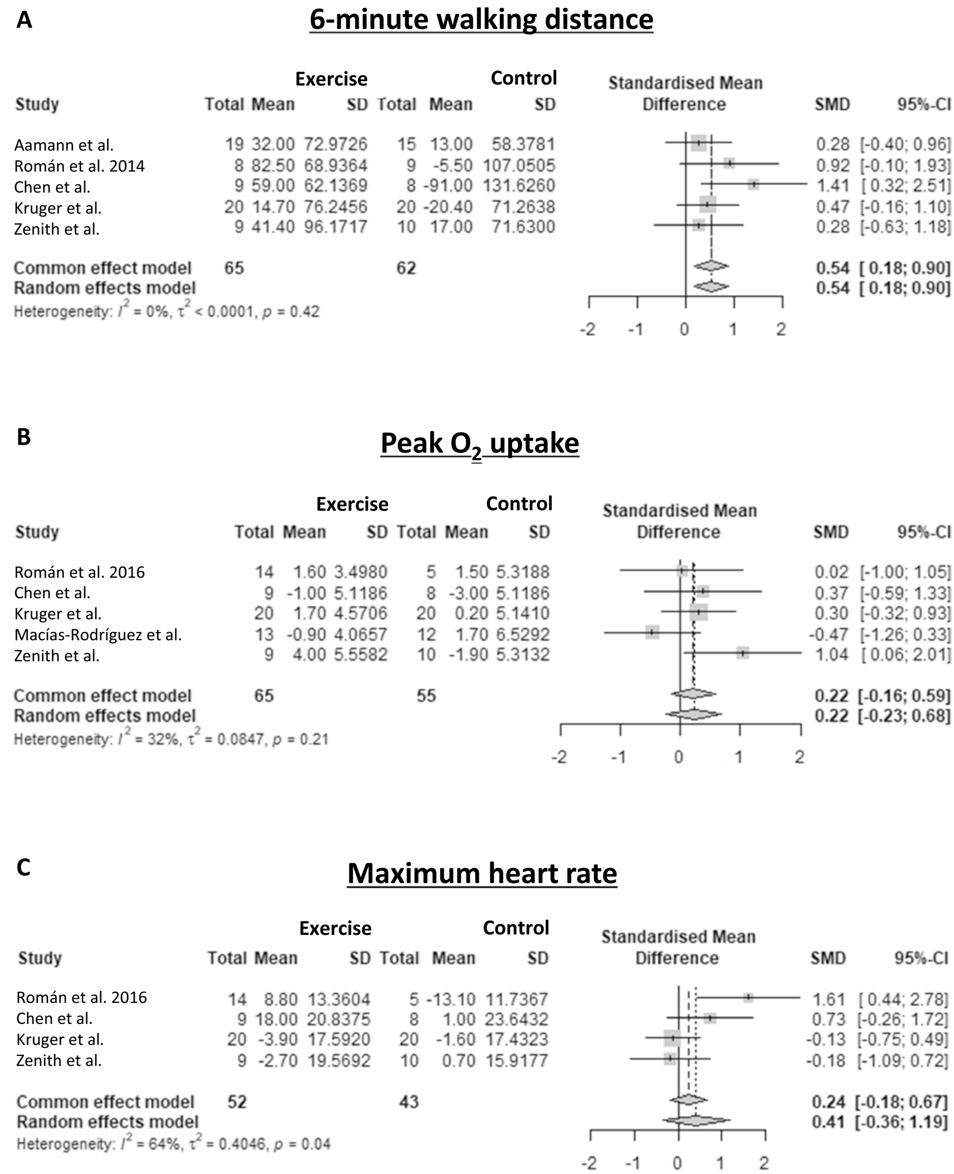


Fig. 4 Forest plot for the effect of exercise on outcomes in patients with liver cirrhosis. **A** 6-min walking distance, **B** peak O_2 uptake, and **C** maximum heart rate. *SMD* standard mean difference, *CI* confidence intervals

CLDQ

There were no significant differences in the changes in CLDQ scores between the exercise and control groups (Fig. 3C).

6MWD, peak O_2 uptake, and maximum heart rate

Five studies examined the 6MWD, and all studies demonstrated an improvement in the 6MWD in the exercise group compared with the control group. Overall, the 6MWD significantly improved in the exercise group compared with the control group (Fig. 4A).

There were no significant differences in peak O_2 uptake or maximum heart rate between the exercise and control groups (Fig. 4B, C).

Analysis 2: meta-analysis of the effect of exercise, including resistance exercise, on outcomes in patients with liver cirrhosis

Serious events

In all five analyzed studies using a combination of aerobic and resistance exercise, the incidence of serious events was 6.25% (7/112) and 24.7% (18/73) in the combination exercise and control groups, respectively. The combination

Table 2 Serious and non-serious events

	Serious events		Non-serious events	
	Exercise group	Control group	Exercise group	Control group
Deaths (*n*)	0	4	Not applicable	Not applicable
Liver-related events (*n*)	6	11	0	1
	Liver transplantation ($n=3$) Ascites requiring paracentesis ($n=2$) Hepatocellular carcinoma ($n=1$)	Liver failure ($n=5$) Liver transplantation ($n=3$) Gastrointestinal bleeding ($n=2$) Hepatocellular carcinoma ($n=1$)		Minimal hepatic encephalopathy requiring treatment with lactulose ($n=1$)
Non-liver-related events (n)	7	9	6	1
	Duodenal ulcer induced by self-prescribed non-steroidal anti-inflammatory drugs ($n=1$) Perianal abscess ($n=1$) Severe hypertension ($n=1$) Commotio ($n=1$) Prostate cancer ($n=1$) Inflammatory bowel disease requiring colectomy ($n=1$) Other surgery ($n=1$)	Infection ($n=3$) Fever of unknown origin ($n=2$) Fracture of the foot ($n=1$) Resurgery of osteosynthesis in column ($n=1$) Apoplexia cerebri ($n=1$) Breast adenocarcinoma ($n=1$)	Infection ($n=2$) Musculoskeletal injury to the knee ($n=1$) Anemia requiring intravenous iron ($n=1$) Knee injury (not during exercise) ($n=1$) Back pain ($n=1$)	Stomatitis (medicine induced) ($n=1$)

exercise group showed an approximately 18% lower incidence of serious events. Overall, the incidence of serious events was significantly lower in the combination exercise group than in the control group (Fig. 5A).

Non-serious events

The incidence of non-serious events was 4.5% (5/112) and 2.7% (2/73) in the combination exercise and control groups, respectively. There was no significant difference in the incidence of nonserious events between the combination exercise and control groups (Fig. 5B).

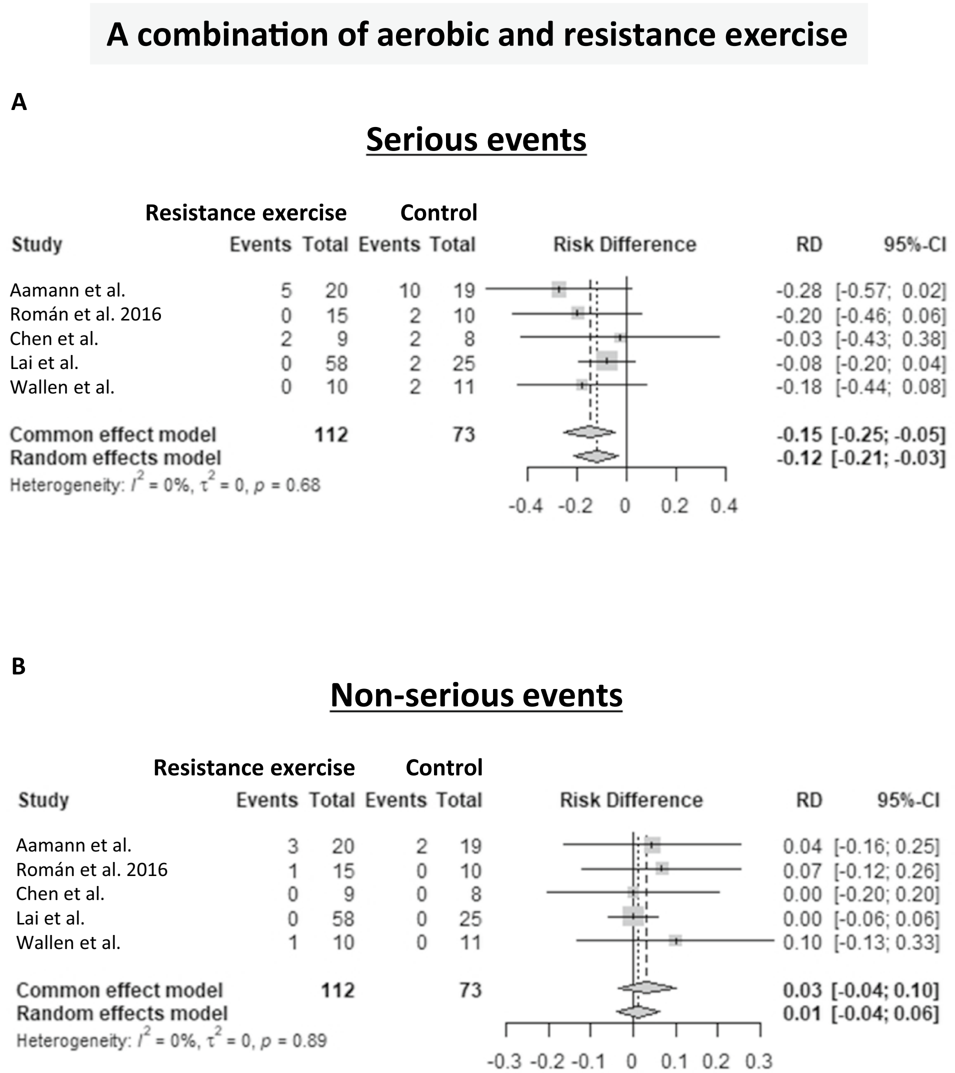
Discussion

This meta-analysis demonstrated that exercise did not negatively affect the incidence of serious or non-serious events, liver function, or patient-reported outcomes. We further found that exercise significantly improved the 6MWD. Moreover, our study is the first to reveal that a combination of aerobic and resistance exercise significantly reduces the incidence of serious events in patients with liver cirrhosis.

Our meta-analysis demonstrated that exercise did not negatively affect the incidence of serious/non-serious events or liver function, as evaluated by Child–Pugh and MELD scores. On the other hand, previous studies reported that exercise causes an increase in portal pressure, a reduction of hepatic blood flow [18], and an impairment in renal function in patients with cirrhosis [19]. These studies suggested a risk of serious adverse events associated with exercise. However, the previous studies were single-arm before-and-after studies conducted in the late 1990s, and the predominant etiology of liver cirrhosis was alcohol consumption, hepatitis B virus, and hepatitis C virus. Our meta-analysis evaluated only RCTs conducted after 2013 and included patients with NASH that exercise is a fundamental therapy. Thus, differences in the study design and etiology of liver cirrhosis may be possible reasons for the discrepancy between previous studies and our meta-analysis. None of the RCTs reported harmful effects of exercise. For aerobic exercise, the median protocol was 60 min/session and 3 times/week for 10 weeks. For a combination of aerobic and resistance exercise, the median protocol was 30 min/session and 3 times/week for 12 weeks.

Exercise therapy is not recommended in cirrhotic patients with Child–Pugh class C in the Evidence-Based Clinical Practice Guidelines for Liver Cirrhosis 2020 co-edited by The Japanese Society of Gastroenterology and The Japan Society of Hepatology [1, 2]. However, after the publication of the guidelines, three RCTs demonstrated no harmful effects of exercise even in patients with cirrhosis, of whom over 50% were Child–Pugh class B/C [17, 20, 29]. The combined data from the three RCTs also showed the incidence of serious events was lower in the exercise group compared to the control group (2.8% [$n=2/71$] vs. 13.5% [$n=5/37$]). Although the duration of exercise was short (8–12 weeks) in the three RCTs, these findings may suggest that suitable exercises tailored for each individual may be feasible and

Fig. 5 Forest plot for the effect of a combination of aerobic and resistance exercise on outcomes in patients with liver cirrhosis. Incidence of **A** serious and **B** non-serious events. *RD* risk differences, *CI* confidence intervals



safe for patients with liver cirrhosis, regardless of disease severity.

We demonstrated that exercise significantly improved the 6MWD. The 6MWD has been reported to correlate with Child–Pugh and MELD scores [7, 8]. The 6MWD has also been reported to be a predictor of clinical decompensation in patients with liver cirrhosis [30]. Moreover, the 6MWD was an independent prognostic factor for patients with liver cirrhosis [6–8]. It remains unclear why 6MWD is associated with various liver-related outcomes. Recently, Duarte-Rojo et al. reported that the 6MWD correlates with the liver frailty index and can be used as a frailty metric in patients with liver cirrhosis [31]. Frailty is associated with an increased risk for serious events in patients with liver cirrhosis [1–4]. Accordingly, the 6MWD may be associated with various liver-related outcomes by reflecting frailty status. In this study, all five RCTs demonstrated a favorable effect of exercise on 6MWD, which may be interpreted as the 6MWD being a useful index for evaluating the effects of exercise in patients with liver cirrhosis. The 6MWD is generally measured by physiotherapists, and collaboration between gastroenterologists and rehabilitation is becoming increasingly important in the management of patients with liver cirrhosis.

To the best of our knowledge, this is the first study to demonstrate that a combination of aerobic and resistance exercise significantly reduces the incidence of serious events in patients with liver cirrhosis. In contrast to aerobic exercise, resistance exercise causes the muscles to contract against external resistance and promotes skeletal muscle hypertrophy [32]. Therefore, resistance exercise is used to improve sarcopenia in patients with various chronic diseases [33]. Sarcopenia is highly prevalent in patients with liver cirrhosis and is a risk factor for various severe events, including liver failure, hepatocellular carcinoma, and infection [34, 35]. Tandon et al. reported that resistance exercise improved sarcopenia in patients with liver cirrhosis [36]. Accordingly, resistance exercise may reduce the incidence of serious events by reducing sarcopenia. Moreover, Tantai et al. performed a meta-analysis and demonstrated that sarcopenia is an independent risk factor for mortality in patients with cirrhosis [5]. In our meta-analysis, three patients died in the control group, while no patients died in the combination exercise group. We could not examine the impact of a combination of aerobic and resistance exercise on mortality owing to the small number of deaths. We also have to be cautious in the interpretation of the results, because of an asymmetrical pattern in the funnel plots. However, these data suggest that a combination of aerobic and resistance exercise may be beneficial in suppressing serious events, leading to improved survival in patients with liver cirrhosis.

This study has several limitations. First, the number of deaths was small owing to the short duration of the study period. Second, exercise therapy was not uniform, and we could not determine the suitable intensity and duration of exercise for patients with liver cirrhosis. Third, we were unable to examine other factors associated with serious events, including malnutrition [37], nutritional therapy, myosteatosis [38], and medications due to the heterogeneity of interventions across the studies. Fourth, no studies provided information about the follow-up period after the intervention, which could affect the onset of events. Thus, further studies should focus on the long-term effects of exercise on prognosis using identical exercise protocols, along with information on malnutrition, nutritional therapy, quality of skeletal muscle, medications, and follow-up periods after the intervention in patients with liver cirrhosis.

This meta-analysis demonstrated no negative impact of exercise on the incidence of serious or non-serious events, liver function, or patient-reported outcomes. In addition, we found that exercise significantly improved the 6MWD, a metric of frailty. Furthermore, we first revealed that resistance exercise in combination with aerobic exercise significantly reduced the incidence of serious events in patients with liver cirrhosis. These results suggest that exercise therapy can be safely administered and may improve frailty in patients with cirrhosis. In particular, a combination of aerobic and resistance exercise may be beneficial in suppressing serious events and improving prognosis in patients with liver cirrhosis.

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Authors' contributions TK and SY participated in the study conception, design, and funding acquisition. TK, SK, KHirota, MT, JT, and HN performed the data searches. TK, RH, DN, TT, MK, SK, KHirota, MT, JT, and HN participated in the data extraction. TK, AK, HM, and KHiraoka performed the quality assessment of the studies. AK and MK performed the analysis. TK, SK, KHirota, MT, JT, HN, HM, KHiraoka, KE, SI, and SY interpreted the data. TK, AK, RH, DN, TT, and MK drafted the manuscript. HM, KHiraoka, KE, SI, and SY participated in the critical revision.

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