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Systematic Reviews

SYSTEMATIC REVIEW UPDATE

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# The effectiveness of exercise prehabilitation on aerobic capacity, muscle strength and body composition in patients with cirrhosis awaiting liver transplantation: a systematic review and meta-analysis protocol

Elelwani Nevhufumba[1*], Demitri Constantinou[1], Devind Peter[2] and Philippe Jean-Luc Gradidge[1]

## Abstract

**Introduction** Cirrhosis is the main cause of morbidity and mortality globally, accounting for approximately 1.2 million deaths annually. Impaired aerobic capacity, muscle wasting and reduced muscle strength are significant complications in patients with cirrhosis. Preoperative exercise intervention "prehabilitation" has been recognised as a potential approach to optimise muscle strength, aerobic capacity and body composition as well as quality of life in patients awaiting abdominal surgery. However, there is little evidence on the effects of preoperative exercise on older adults with cirrhosis and awaiting liver transplant. Thus, the primary objective of this systematic review and meta-analysis will be to assess the effects of exercise interventions in improving aerobic capacity, muscle strength and body composition of older adults with cirrhosis and awaiting liver transplant.

**Methods and analysis** This systematic review and metaanalysis protocol was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This systematic review will include all peer-reviewed randomised controlled trials (RCTs), including cluster RCTs, controlled (non-controlled), complex clinical trials (CCTs) or cluster trials, cohort, observational studies published in English from inception until July 2024. The following electronic databases will be searched: MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (EBSCO) and Scopus (Elsevier) and supplemented by a secondary screening of the reference lists of all included articles. Searches will involve studies with both male and female participants aged ≥ 18 years with cirrhosis and awaiting liver transplant. Primary outcomes will include muscle strength, and aerobic capacity. The secondary outcomes include body composition (e.g. body mass index, and thigh circumference). The Cochrane Collaboration Risk of Bias Tool will be used to evaluate quality of the studies and Review Manager (RevMan) V.5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Effect sizes will be expressed as a standardised mean difference, and their 95% confidence intervals will be calculated and presented as a forest plot. The standard $\chi^2$ and $I^2$ tests will be used to test heterogeneity.

**Conclusion** This systematic review and meta-analysis is anticipated to provide meaningful and contemporary evidence on the effects of preoperative exercise in older adults living with cirrhosis and awaiting liver transplant. In

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addition, the findings will help clinicians with developing safe and effective preoperative exercise regimens for these patients.

**Keywords** Cirrhosis, Prehabilitation, Preoperative exercise, Liver transplantation

**Systematic review registration** PROSPERO CRD42021290618

## Introduction

Cirrhosis, also known as liver cirrhosis or end-stage liver disease (ESLD), refers to liver function impairment that results from fibrosis due to damage from liver disease [1]. In 2017, the worldwide prevalence of people living with cirrhosis was more than 160 million [2] and accounted for 1.32 million deaths in that year [3]. Liver transplantation has become the treatment of choice for patients with ESLD [4] and who meet the Milan criteria for cirrhosis and hepatocellular carcinoma (HCC) [5].

Presently, there are two commonly utilised prognostic instruments are the quantitative Child-Turcotte Pugh (C-T) score, also referred to as the Child-Pugh (C-P), and the model for end-stage liver disease (MELD) score [6]. The MELD score was initially developed to predict survival post-transjugular intrahepatic portosystemic shunt procedure [7]. It was also used to prioritise liver transplantation recipients and predict 3-month survival in patients with cirrhosis [8]. However, MELD is not a reliable indicator of survival following transplantation [9]. Contrary, the CPS was designed to determine the operative risk for patients having portosystemic surgery for variceal hemorrhage . Moreover, the CPS predicts the development of complications, response of patients to surgical procedure [8], as well as predicting mortality in patients with cirrhosis[10].

Patients with cirrhosis have comorbidities such as malnutrition, impaired exercise capacity and physical frailty [11]. Cirrhosis is a complex condition that includes a decrease in muscle strength and mass, elevated proinflammatory cytokines, anorexia and fatigue, resulting in sarcopenia [12], reduced maximal oxygen consumption ($VO_2$max) [13], impaired pulmonary gas exchange [13] and functional capacity [14]. It is established that these factors lead to lower survival rates, greater risk of being removed from transplant lists and increased risk for pretransplant mortality [15], higher rates of cirrhosis-related complications and infections and worse outcomes postliver transplantation [16], such as prolonged length of in-hospital stay and mortality [14]. These complications compromise health-related quality of life (HRQOL) [11] and are associated with severity of cirrhosis [17]. Peak exercise oxygen consumption ($VO_2$peak) is associated with severity of liver disease and independently associated with shorter survival after liver transplantation [14].

Exercise ability in these patients may be affected by fatigue, ascites and bleeding [18]. Notwithstanding that, studies have indicated possible benefits of preoperative exercise ("prehabilitation") in improving patients' functional ability before surgery and reducing postoperative complications [19]. Although physical activity is recognised as important pre- and post-transplant, there are no established guidelines or recommendations [20]. Despite several studies showing beneficial effects, there has been debate regarding the safety of exercise in patients with advanced cirrhosis due to the possibility of elevated portal pressures during the activity and possible risk of hepatic encephalopathy and variceal haemorrhage [20].Recently, Berzigotti et al. investigated the effect of weight loss and leptin on hepatic venous pressure gradient (HVPG) after a 16-week gym-based exercise and observed ≥10% decrease in HPVG in approximately 42% of the population. Zenith et al. offered supervised exercise training in patients with cirrhosis and found that the programme increased aerobic capacity and muscle mass and decreased fatigue [21].

A home-based exercise programme was made available in RCTs by Williams et al. for patients awaiting liver transplantation, and the programme demonstrated an improved exercise capacity and was both safe and feasible [22]. Debette-Gratien et al. offered supervised aerobic and resistance training to 13 liver transplantation recipients and found that personalised and standardised physical activity was safe, effective, well-tolerated and led to improved quality of life and maximal functional exercise capacity as well as muscle strength [23]. Román and colleagues reported that moderate exercise in patients with cirrhosis enhances muscle mass and effort tolerance while decreasing body fat and risk of falls [24]. Most studies describing prehabilitation in liver transplantation recipients have shown promising results. In order to enhance the quality of life for those already experiencing cirrhosis-related deterioration, it is necessary to evaluate the current, feasible intervention as research presses toward the cure for cirrhosis. The primary objective of the present systematic review and meta-analysis is to assess the effects of preoperative exercise programmes on aerobic capacity (VO2max), functional capacity, muscle strength,

sarcopenia, frailty and health-related quality of life in adults with cirrhosis.

## Review questions

What is the status of current knowledge in the published literature about the effectiveness of prehabilitation on cardiovascular health, health-related physical fitness, and frailty in patients with cirrhosis waiting for liver transplantation and the various settings in which exercise can be performed?

## Methods

### Design

This systematic review will be conducted according to the Cochrane Handbook [25] and in accordance with the guidelines of the Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) declaration [26]. This proposed systematic review will be written according to PRISMA-P statement (Additional file 1) and is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021290618).

### Eligibility criteria

#### *Types of studies*

All peer-reviewed randomised controlled trials (RCTs), including cluster RCTs, controlled (non-controlled) clinical trials (CCTs) or cluster trials, cohort, observational studies that addresses the research questions. Individual case reports, review papers, editorials and conference abstracts with no subsequent peer reviewed full-text paper will be excluded. We will exclude any paper that is not written in English, unless provided with a translated manuscript by the authors.

### Participants

The review will consider all studies that include adult patients ($\geq$ 18 years old) with cirrhosis and waiting for liver transplantation. No limitations will be placed on programme duration, delivery method, intensity, geographical location, gender, ethnicity, duration of illness and nationality.

### Interventions

This review will consider cirrhosis prehabilitation programmes including exercise as the major component. Prehabilitation is defined as the practice of strengthening a patient's functional capacity before surgery with the goal of improved postoperative outcomes [27]. Exercise is a type of physical activity that is planned, structured and repetitive with the enhancement or maintenance of physical fitness as its ultimate or intermediate goal. Various training modalities, including Yoga, Qigong and Tai chi, as well as resistance, aerobic and flexibility training, can be used as part of an exercise intervention during a prehabilitation programme. There will be no restrictions on the environment (land-based or aquatic training), materials used, and type of exercise.

### Comparators

We will include comparator interventions defined as preoperative exercise also named preoperative rehabilitation. We defined preoperative exercise as a regimen of physical activity, which can include individualised, home-based, or supervised physical exercise training programmes.

### Outcomes

We will include studies that report on primary health outcomes and secondary outcomes. The primary outcomes include physical and functional capacity, muscle strength, aerobic function, sarcopenia, frailty and health-related quality of life. The secondary outcomes include body composition (weight, waist circumference, body mass index, body fat % and thigh circumference), lipids profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and/or triglycerides), waist circumference and blood pressure.

### Search strategy

The search strategy will aim to locate both published and unpublished studies. We will conduct a systematic search following Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions [25]. An initial limited search will be conducted in PubMed using the keywords "cirrhosis," "prehabilitation," "preoperative exercise" and "liver transplantation" and their synonyms. The text words in the titles and abstracts used in the retrieved articles as well as the index terms used to describe the articles will be used to develop a full search strategy (Table 1). The search strategy will be adapted for each included database. The databases to be searched include PubMed, MEDLINE via EBSCO, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and Scopus via Elsevier. The search for unpublished studies and grey literature will include Scopus and the ProQuest Dissertations and Theses Global database. An electronic database search will be performed by searching titles, abstracts, keywords and subheadings for articles published up to 2023.

**Table 1** Search strategy

MEDLINE

1. ("liver cirrhosis" [MeSH Terms] OR ("liver" [All Fields] AND "cirrhosis" [All Fields]) OR "liver cirrhosis" [All Fields]) AND ("preoperative exercise" [MeSH Terms] OR ("preoperative" [All Fields] AND "exercise" [All Fields]) OR "preoperative exercise" [All Fields]) AND ("liver transplantation" [MeSH Terms] OR ("liver" [All Fields] AND "transplantation" [All Fields]) OR "liver transplantation" [All Fields])

2. ("preoperative exercise" [MeSH Terms] OR ("preoperative" [All Fields] AND "exercise" [All Fields]) OR "preoperative exercise" [All Fields]) AND (("orthotopic" [All Fields] OR "orthotopical" [All Fields] OR "orthotopically" [All Fields]) AND ("transplantability" [All Fields] OR "transplantable" [All Fields] OR "transplantated" [All Fields] OR "transplantating" [All Fields] OR "transplantation" [MeSH Terms] OR "transplantation" [All Fields] OR "transplantations" [All Fields] OR "transplanted" [All Fields] OR "transplanting" [All Fields] OR "transplantation" [MeSH Subheading] OR "transplantations" [All Fields] OR "transplanter" [All Fields] OR "transplanters" [All Fields] OR "transplantion" [All Fields] OR "transplants" [MeSH Terms] OR "transplants" [All Fields] OR "transplant" [All Fields]))

3. ("preoperative exercise" [MeSH Terms] OR ("preoperative" [All Fields] AND "exercise" [All Fields]) OR "preoperative exercise" [All Fields]) AND ("liver transplantation" [MeSH Terms] OR ("liver" [All Fields] AND "transplantation" [All Fields]) OR "liver transplantation" [All Fields])

Translations

preoperative Exercise: "preoperative exercise" [MeSH Terms] OR ("preoperative" [All Fields] AND "exercise" [All Fields]) OR "preoperative exercise" [All Fields]

liver transplantation: "liver transplantation" [MeSH Terms] OR ("liver" [All Fields] AND "transplantation" [All Fields]) OR "liver transplantation" [All Fields]

4. ("preoperative exercise" [MeSH Terms] OR ("preoperative" [All Fields] AND "exercise" [All Fields]) OR "preoperative exercise" [All Fields] OR ("rehabilitant" [All Fields] OR "rehabilitants" [All Fields] OR "rehabilitate" [All Fields] OR "rehabilitated" [All Fields] OR "rehabilitates" [All Fields] OR "rehabilitating" [All Fields] OR "rehabilitation" [MeSH Terms] OR "rehabilitation" [All Fields] OR "rehabilitations" [All Fields] OR "rehabilitative" [All Fields] OR "rehabilitation" [MeSH Subheading] OR "rehabilitations" [All Fields] OR "rehabilitational" [All Fields] OR "rehabilitator" [All Fields] OR "rehabilitators" [All Fields])) AND ("liver cirrhosis" [MeSH Terms] OR ("liver" [All Fields] AND "cirrhosis" [All Fields]) OR "liver cirrhosis" [All Fields] OR "cirrhosis" [All Fields] OR "fibrosis" [MeSH Terms] OR "fibrosis" [All Fields]) AND ("liver transplantation" [MeSH Terms] OR ("liver" [All Fields] AND "transplantation" [All Fields]) OR "liver transplantation" [All Fields])

5. ("preoperative exercise" [MeSH Terms] OR ("preoperative" [All Fields] AND "exercise" [All Fields]) OR "preoperative exercise" [All Fields] OR ("rehabilitant" [All Fields] OR "rehabilitants" [All Fields] OR "rehabilitate" [All Fields] OR "rehabilitated" [All Fields] OR "rehabilitates" [All Fields] OR "rehabilitating" [All Fields] OR "rehabilitation" [MeSH Terms] OR "rehabilitation" [All Fields] OR "rehabilitations" [All Fields] OR "rehabilitative" [All Fields] OR "rehabilitation" [MeSH Subheading] OR "rehabilitations" [All Fields] OR "rehabilitational" [All Fields] OR "rehabilitator" [All Fields] OR "rehabilitators" [All Fields])) AND ("liver cirrhosis" [MeSH Terms] OR ("liver" [All Fields] AND "cirrhosis" [All Fields]) OR "liver cirrhosis" [All Fields]) AND ("liver transplantation" [MeSH Terms] OR ("liver" [All Fields] AND "transplantation" [All Fields]) OR "liver transplantation" [All Fields])

6. ("preoperative exercise" [MeSH Terms] OR ("preoperative" [All Fields] AND "exercise" [All Fields]) OR "preoperative exercise" [All Fields] OR ("rehabilitant" [All Fields] OR "rehabilitants" [All Fields] OR "rehabilitate" [All Fields] OR "rehabilitated" [All Fields] OR "rehabilitates" [All Fields] OR "rehabilitating" [All Fields] OR "rehabilitation" [MeSH Terms] OR "rehabilitation" [All Fields] OR "rehabilitations" [All Fields] OR "rehabilitative" [All Fields] OR "rehabilitation" [MeSH Subheading] OR "rehabilitations" [All Fields] OR "rehabilitational" [All Fields] OR "rehabilitator" [All Fields] OR "rehabilitators" [All Fields])) AND ("liver cirrhosis" [MeSH Terms] OR ("liver" [All Fields] AND "cirrhosis" [All Fields]) OR "liver cirrhosis" [All Fields]) AND (("orthotopic" [All Fields] OR "orthotopical" [All Fields] OR "orthotopically" [All Fields]) AND ("transplantability" [All Fields] OR "transplantable" [All Fields] OR "transplantated" [All Fields] OR "transplantating" [All Fields] OR "transplantation" [MeSH Terms] OR "transplantation" [All Fields] OR "transplantations" [All Fields] OR "transplanted" [All Fields] OR "transplanting" [All Fields] OR "transplantation" [MeSH Subheading] OR "transplantations" [All Fields] OR "transplanter" [All Fields] OR "transplanters" [All Fields] OR "transplantion" [All Fields] OR "transplants" [MeSH Terms] OR "transplants" [All Fields] OR "transplant" [All Fields]))

### Study selection

Titles and abstracts of the studies identified will be screened by two independent reviewers (EN and DP) for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full, and their citation details imported into the JBI System for the Unified Management, Assessment, and Review of Information (JBI SUMARI; JBI, Adelaide, Australia). The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Disagreement will be solved by the application of criteria, discussion and consensus. Where no consensus can be reached a third reviewer (DC) will be consulted. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Fig. 1)..

### Data extraction

Two reviewers (EN and DP) will independently extract the data from the selected studies into a standardised form in Microsoft Excel Spreadsheet. Data extracted will include the following: population interventions, comparators, outcomes, setting and study design (Table 2). This tool will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full systematic review. In the case of missing, incomplete or ambiguous data, the authors of the study will be contacted for clarification. If additional data or clarification is required, the authors of the papers will be contacted. Disagreements will be resolved by reaching a consensus.

### Risk of bias assessment

Two reviewers (EN and DP) will independently use the Cochrane "Risk of bias" tool described in the Cochrane Handbook for Systematic Reviews Interventions [25] to assess the risk of bias. The risk of bias will judge them as either low risk of bias, some concerns or high risk of bias. The following domain will be assessed: allocation,

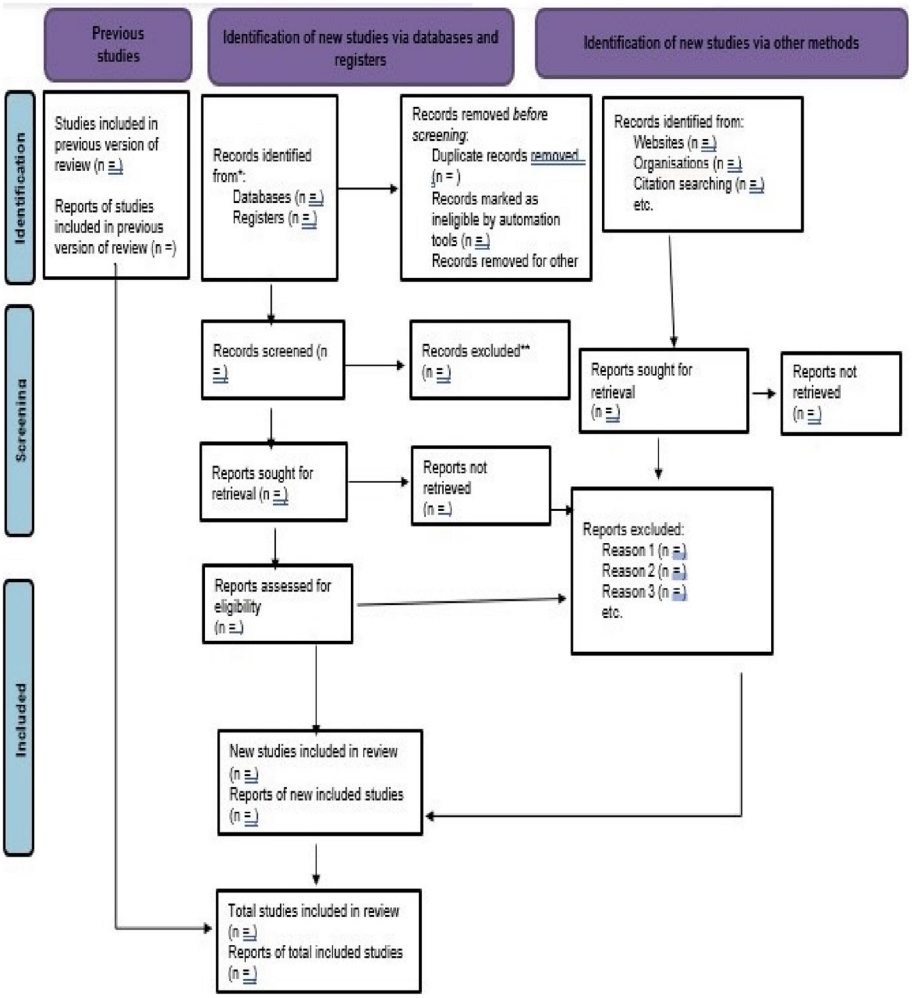



**Fig. 1** PRISMA flow chart

outcome assessors, incomplete outcome data, baseline outcome measurements, knowledge of allocated intervention (blinding), selective outcome reporting and randomisation procedures.

### Data synthesis

The extracted data will be presented in tabular, diagrammatic or figure form in a manner that aligns with the objective of this systematic review and will be supported by narrative descriptions of the data. A meta-analysis will be carried out using Review Manager (RevMan) V.5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Effect sizes will be expressed as a standardised mean difference, and their 95% confidence intervals will be calculated and presented as a forest plot. The standard $\chi^2$ and $I^2$ tests will be used to test heterogeneity. If the chi-square test is significant below $p = 0.05$, we will quantify the amount of heterogeneity using $I^2$ statistics. We will consider $I^2$ above 50% as indicative of substantial heterogeneity. If data cannot be meta-analysed, we will summarise the articles ad conclude on high-quality studies. Subgroup analysis will be conducted by splitting the participant data into subgroups to make comparisons between them.

### Publication bias

Publication of bias will be examined using Egger's linear regression test for funnel plot asymmetry [28]. Duval and Tweedie's trim and fill will be conducted if there is evident publication bias.

### Grading of evidence

Overall quality of the evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [29] by two independent

**Table 2** Data extraction instrument

| | |
|---|---|
| Bibliographic | Name of first author |
| | Year of publication |
| | Title |
| | Country |
| Setting | Hospital |
| | Home-based |
| | Community |
| | University laboratory |
| | Urban/rural |
| Study design | Randomised control trials (RCTs) |
| | Non-RCTs |
| | Observational |
| | Clinical trial |
| Study population | Sex |
| | Age |
| | Sample size |
| | Exercise group |
| | Controlled group |
| | Body mass index |
| | Child-pugh score (CPS) |
| | Model for End-stage Liver Disease (MELD) score |
| | Diagnosed with cirrhosis |
| Exercise intervention | Frequency |
| | - Number of sessions per week |
| | Intensity |
| | - Rate of perceived exertion |
| | - Heart rate max (%) |
| | Duration |
| | - Intervention duration |
| | - Exercise duration per week |
| | Type |
| | - Aerobic and resistance exercises i.e. weights, bands, cycle ergometer, treadmill, or elliptical bike |
| | Site |
| | - Hospital |
| | - Homebased |
| | Supervision |
| | - Unsupervised |
| | - One-on-one |
| | - Group class |
| | - Video call/audio |
| | Adherence |
| | - Full adherence, partial adherence (%) |

**Table 2** (continued)

| | |
|---|---|
| Outcomes assessed | Muscle strength |
| | - Handgrip dynamometer |
| | - Isokinetic machine |
| | Muscle mass |
| | - Dual energy x-ray absorptiometry |
| | - Cross-sectional area |
| | - Computed tomography |
| | - Bioelectrical impedance analysis |
| | Aerobic capacity |
| | - Cardiopulmonary exercise testing |
| | - 6-minute walking distance |
| | Health related quality of life |
| | - Chronic liver disease questionnaire |
| | - 5-Dimension 5-Level questionnaire |
| | - EuroQol visual analogue scale questionnaire |
| | - Short-form-36 questionnaire |
| | - Short-form-8 questionnaire |
| | Frailty |
| | - Liver frailty index: balance; handgrip strength; and chair stand test; safety; liver function and cognitive performance |
| Study results | Baseline measures |
| | Follow up measures |
| | Significant differences (outcomes) |
| | Significant differences between groups |

reviewers. The evidence will then be classified as high, moderate, low or very low.

## Discussion and implications of the review

Prehabilitation in patients awaiting liver transplantation may enhance aerobic and functional ability, and more crucially, prehabilitation may prevent the decline in aerobic and functional capacity. In patients preparing for abdominal surgery, prehabilitation may facilitate improvements in physical function, cardiorespiratory fitness and muscle strength in the preoperative period. Prehabilitation is associated with a low incidence of postoperative complications and a shorter length of hospital stay following liver transplantation. Exercise therapists could provide various prehabilitation programmes to patients who are waiting for liver transplantation. The review will provide known evidence of prehabilitation for patients awaiting liver transplantation in the identified primary and secondary outcomes. It will also identify the gaps in this area of research and inform future research.

**Abbreviations**

| | |
|---|---|
| CCTs | Controlled clinical trials |
| CENTRAL | Cochrane Central Register of Control Trials |
| CINAHL | Cumulative Index to Nursing and Allied Health Literature |
| CPS | Child-Pugh score |
| ESLD | End-stage liver disease |
| HCC | Hepatocellular carcinoma |
| HRQOL | Health-related quality of life |
| HVPG | Hepatic venous pressure gradient |
| MEDLINE | Medical Literature Analysis and Retrieval System Online |
| MELD | Model for end-stage liver disease |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analysis |
| PRISMA-P | Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols |
| PROSPERO | International Prospective Register of Systematic Reviews |
| RCTs | Randomised control trials |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02608-y.

Supplementary Material 1. PRISMA-P 2015 Checklist.

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Not applicable.

**Authors' contributions**
EN carried out the initial background research. EN also drafted the manuscript. DC and PJG critically revised the manuscript and approved the final version. EN and DP contributed to the development of the selection criteria, the risk of bias assessment and data extraction criteria.

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**Availability of data and materials**
Not applicable.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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