Association of sarcopenia with liver fibrosis and steatohepatitis in non-alcoholic fatty liver disease: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disorder over the last four decades, more evidence shows a high prevalence of sarcopenia in NAFLD that may influence disease severity. This meta-analysis aims to determine the association of sarcopenia with liver fibrosis and steatohepatitis in NAFLD.

Methods and analysis We will conduct the literature search using Medline (via PubMed), Web of Science databases, EMBASE, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews (from the date of inception to 1 May 2022). There will be no restriction to the publication year. Two reviewers will independently screen the articles and abstract key study characteristics. The outcome of this meta-analysis is the strength of association of sarcopenia with liver fibrosis and steatohepatitis in NAFLD.

Ethics and dissemination There will be no need of ethics approval as this systematic review is summary and analysis of existing literature. Final results may be presented in international conferences or a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis will incorporate the latest research in order to obtain a comprehensive and objective result, which could provide further insights into risk stratification and assessment of disease severity for non-alcoholic fatty liver disease (NAFLD).

⇒ The study will employ a rigorous search strategy following the gold-standard methodology for systematic review, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

⇒ Selection of studies, data extraction and assessment of bias will be done independently by two reviewers, any inconsistencies will be worked out by a third reviewer.

⇒ The different diagnosis methods of NAFLD and the definition of sarcopenia may result in increased risk of publication bias.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), defined as hepatic steatosis on imaging or histology in the absence of identified causes, has become the most common chronic liver disorder over the last four decades. NAFLD is currently the most rapidly increasing cause of liver-related mortality worldwide and is emerging as an important cause of end-stage liver disease and primary liver cancer. Beyond that, patients with NAFLD, particularly those with clinically significant fibrosis, have a higher risk of severe COVID-19 than those without the disease. Patients with NAFLD attain a 1.9-time higher risk of incident cancers than the general population, particularly cancers involving the liver, gastrointestinal tract and uterus.

Sarcopenia has been linked to NAFLD in epidemiological research based on meta-analyses, suggesting sarcopenia as a novel risk factor for NAFLD. Sarcopenia is characterised by generalised and progressive loss of skeletal muscle mass and strength, frequently associated with poor quality of life, physical disability and death. Sarcopenia has been linked to an increased risk of diabetes, dyslipidaemia, cardiovascular disease and liver disease.

NAFLD comprises a wide spectrum of disease including simple steatosis, non-alcoholic steatohepatitis (NASH), from liver fibrosis to cirrhosis, liver failure and hepatocellular carcinoma. The assessment of histological severity in NAFLD patients is critical for identifying high-risk subjects and determining the optimal time to commence medical interventions. In recent years, studies...
have emerged examining the relationship of sarcopenia with liver fibrosis and steatohepatitis in NAFLD, therefore, we perform this meta-analysis to determine the association of sarcopenia with liver fibrosis and steatohepatitis in NAFLD in order to obtain a comprehensive and objective result.

 METHODS
This study's protocol has been registered within the International Prospective Register of Systematic Review (PROSPERO) database (registration number CRD42022322685). It is reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (see online supplemental file 1 PRISMA-P checklist).9 This systematic review will be conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Any amendments made to this protocol and the whole review process will update timely on the PROSPERO registration and the final manuscript.

Criteria for considering studies for this review
Types of Studies
Each related case-control, cross-sectional or cohort studies evaluating the association of sarcopenia with liver fibrosis and steatohepatitis in NAFLD will be included. All studies must be published in English. Other types of studies including case series and case reports will be excluded.

Types of Participants
Patients who were diagnosed with NAFLD and sarcopenia. NAFLD will be defined as the presence of ≥5% macrovesicular steatosis. NASH will be diagnosed based on an overall pattern of histological hepatic injury consisting of macrovesicular steatosis, inflammation or hepatocellular ballooning according to Brunt et al's criteria.10 The Sarcopenia Index (SI) will be calculated as follows: SI=total appendicular skeletal muscle mass (kg)/body mass index (kg/m²); this was the official definition provided by a recent consensus meeting known as the 'Foundation for the National Institutes of Health Sarcopenia Project'. Sarcopenia will be defined as SI <0.789 in men or SI <0.512 in women.11

Outcome measures
The outcome of this meta-analysis is the strength of association between the sarcopenia and grades of fibrosis or NASH in NAFLD patients. Pooled adjusted OR with 95% CI will be calculated for analysis. If sufficient data are available, we will analyse whether the independent association will be consistently maintained by adjusting for confounding covariates that affect liver fibrosis.

Information sources and search strategy
We will conduct the literature search using Medline (via PubMed), Web of Science databases, EMBASE and The Cochrane Library. A comprehensive systematic literature search will be performed to identify related studies that assess the association of sarcopenia with steatohepatitis and liver fibrosis in NAFLD. The search will include all articles from inception to April 2022. We will conduct the search by combining medical subject headings and its entry terms. Detailed search strategy was shown in online supplemental file 2.

Data collection and analysis
Selection of Studies
Two reviewers (SL and KW) will independently screen the articles according to the above criteria. In the initial screening, duplicate studies will be eliminated. Then reviewers will determine whether the study could be included through title and abstract according to the above criteria. And by evaluating the full text of the initial selection of articles, exclude the articles that do not meet the criteria. For full text with exclusion criteria, a reason for exclusion will be recorded (eg, language; conference abstracts; full text could not be obtained; insufficient data). At each screening and assessment phase, studies in which a consensus is not reached will be resolved by a third reviewer (DL). If several studies present data from the same study population or multiple publications from the same study are published in chronological order, the study with the largest sample size will be reserved.

Data extraction and management
A standardised electronic form for data extraction will be created by ZW. Two reviewers (JW and MZ) will abstract key study characteristics of selected publications, including country, publication year, participant characteristics (age, sex, country), study design, methods used to identify and verify sarcopenia, NAFLD, NASH and liver fibrosis, adjusted effect estimates with 95% CI and covariates that will be adjusted in multivariable analysis. To ensure accuracy, any inconsistencies will be worked out by a third reviewer (SL). And we will try to contact the study authors by email or post for further information in case of any ambiguity or insufficient information.

Assessment of Risk of Bias and quality of evidence assessment
Two reviewers (ZW and DL) will independently assess risk of bias, and conflicts will be resolved by consultation with a third researcher (KL) or by group discussion. The risk of bias will be divided into three levels: ‘low risk’, ‘high risk’ and ‘unclear risk’.12 Considering that this study is to explore the association between sarcopenia and the histological severity of NAFLD, most of the included studies may be cross-sectional studies, hence, the Newcastle-Ottawa Scale will be used to assess the risk of bias. We will assess the quality of evidence according to Grades of Recommended Assessment, Development and Evaluation classification method, the strength of the body of evidence will be divided into four levels: very low, low, medium and high quality.13
Data synthesis and analysis
Included studies will be presented in a table to summarise characteristics. We will use the standard meta-analysis software (RevMan V.5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The outcome measure of the meta-analysis will be conducted in two aspects. We will quantify the association between the risk of NASH and sarcopenia. Next, we will assess the risk of liver fibrosis in NAFLD patients with sarcopenia compared with NAFLD patients without sarcopenia. The most fully adjusted OR and its 95% CI will be pooled by the generic inverse variance method of DerSimonian and Laird.14 If possible, missing outcome data such as SD will be calculated from the available data (p values, t-values, CI or SEs) using formulas recommended in The Cochrane Handbook.12 Forest plots will be used to visualise pooled estimates. I² statistic and Cochrane Q statistic tests are employed to assess heterogeneity. Heterogeneity assessment allows authors to gauge the feasibility to pool the data, and to perform meta-analysis. If I² is higher than 50%, it will be considered as substantial heterogeneity, and the sources of heterogeneity will be explored by sensitivity analyses. A funnel plot15 and Egger test16 will be used to assess publication bias. If sufficient data are available, a subgroup analysis will be performed based on the diagnostic methods of NAFLD and sarcopenia.

Patient and public involvement
As the present study is a systematic review based on published data, patient and the public are not involved in the study design, conduct, data analysis and result dissemination.

DISCUSSION
The literature has demonstrated a higher risk of NAFLD in individuals with sarcopenia.17–19 Although cirrhotic consequences and hepatocellular carcinoma occur in less than 10% of people with NAFLD in the 10–20 years after diagnosis, the absolute numbers are significant considering the high disease incidence.20,21 Patients with NASH and liver fibrosis have quite significant healthcare consumption and spending.22,23 The objective of our study is to determine the association of sarcopenia and liver fibrosis and steatohepatitis in NAFLD, which could provide important data to collect in future intervention or treatment studies.

Moreover, sarcopenia and NAFLD share the common denominators such as obesity, metabolic risk factors, chronic inflammation, insulin resistance and so on.24 Thus, we intend to explore through this research whether the relationship between sarcopenia and the histological severity of NAFLD still persist after adjusting for above confounding factors. The following limitations of the study need to be considered: the different diagnoses methods of NAFLD and the definition of sarcopenia may result in increased risk of publication bias. Causality may be difficult to establish since most studies are expected to be observational. And the accuracy of conclusions may be biased due to language limitations as well as quality of the original research included. In general, our findings will provide further insights into risk stratification and assessment of disease severity for NAFLD.

Ethics and dissemination
This article does not require the approval of ethical board as it relies on published studies. Study findings will be presented at international conferences and published on a peer-reviewed journal.

Contributors ZW developed the initial idea for this study. MZ, SL and DL developed and revised the search strategy. SL and KL finished the study design. JW, DL and KL were consulted about clinical issues. ZW and KW contributed to the original draft. ZW, SL and JW were responsible for the revision of the draft. ZW, SL and KW are joint first authors. All of the authors approved the final work prior to submission.

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Competing interests None declared.

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