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Protocol for a case–control prospective study to investigate the impact of Hepatic Encephalopathy on Nutritional Intake and Sarcopenia status in patients with end-stage LIVer disease: HENS-LIV study

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ABSTRACT

Introduction Hepatic encephalopathy (HE) is a debilitating symptom of end-stage liver disease (ESLD), but there remains a paucity of evidence regarding its impact on nutritional status, nutritional intake, compliance with nutritional support and resultant muscle health and function. Malnutrition and sarcopenia are associated with increased morbidity and mortality in patients with ESLD. The aim of the current case–control study is to prospectively investigate the impact of HE on nutritional intake and sarcopenia status in patients with ESLD.

Methods and analysis Patients with ESLD, with HE (n=10) and without HE (n=10) will be recruited at the outpatient liver unit, University Hospital Birmingham, UK. All patients will undergo clinical assessment at baseline and again at 6–8 weeks (in-line with their routine clinical follow-up), to assess the impact of HE on reported nutritional intake, nutritional status and sarcopenia/physical functional status. Standard medical, dietetic and home-based exercise physiotherapy care will continue for all participants as determined by their clinical team. Two methods of assessing nutritional intake will include the 24-hour food recall and 3-day food diaries. Assessment of sarcopenia status will be undertaken using anthropometry (mid-arm muscle circumference (MAMC)) and ultrasound imaging of the quadriceps muscle group. Markers of physical function (hand grip strength; chair rise time), frailty (Liver Frailty Index (LFI)), physical activity (accelerometery) and exercise capacity (Duke Activity Status Index (DASI)) will be assessed at both clinic visits.

Ethics and dissemination The study is approved by Wales Research Ethics Committee 2 and Health Research Authority (REC reference: 21/WA/0216). Recruitment into the study commenced November 2021. The findings will be disseminated through peer-reviewed publications and international presentations.

Trial registration number RRK7156.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hepatic encephalopathy (HE) is a debilitating symptom of end-stage liver disease known to exacerbate sarcopenia and frailty which in turn increases morbidity and mortality. There is a lack of prospective research in this area, thus the true impact is not known, and current assessment methods are inadequate.

WHAT THIS STUDY ADDS

⇒ This is a novel study investigating the impact of HE on patient-reported nutritional intake, nutritional and sarcopenia/functional status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will improve understanding of how to assess nutritional and sarcopenia status of this vulnerable patient group and will provide further guidance on areas of unmet research need in this cohort.

INTRODUCTION

Sarcopenia (loss of muscle mass/strength) and reduced physical function are major complications of end-stage liver disease (ESLD), with an increase in prevalence as disease progresses.[1] The causes of sarcopenia and associated reduced physical function in ESLD are multifactorial, including[2–4]:

1. Age-related loss of muscle motor units.
2. Hormonal and immune dysregulation.
3. Malnutrition (poor intake±absorption).
4. Systemic inflammation.
5. An imbalance between protein synthesis and breakdown (catabolism).
6. Reduced physical activity (secondary to hepatic encephalopathy (HE)).

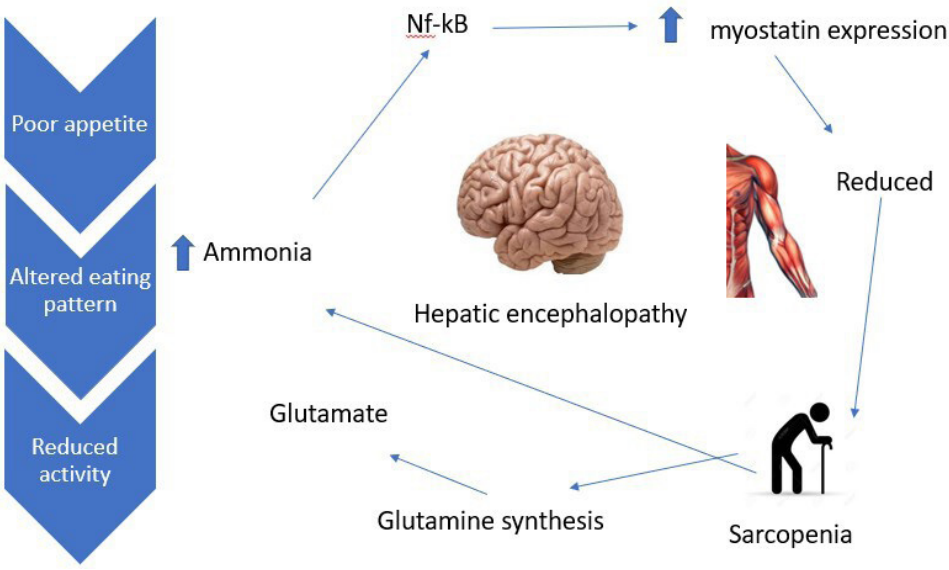

Figure 1 Two-way challenge of sarcopenia and hepatic encephalopathy (HE). The bidirectional relationship between HE, sarcopenia, reduced functional status and altered oral intake. NF-κB, nuclear factor kappa B.

7. Ascites, fatigue, depression.

Sarcopenia and poor physical function are associated with increased all-cause mortality in ESLD, as well as prolonged hospital admissions, infections and worsening hepatic decompensation (eg, ascites and HE).[5–7] Such decompensations in turn, promote a vicious cycle of worsening malnutrition, functional status and disability.

HE affects up to 40% of individuals with ESLD, manifesting as a wide spectrum of neurological or psychiatric abnormalities.[8 9] It is caused by multiple mechanisms, notably hepatic function insufficiency (lack of ammonia clearance) and portosystemic shunting.[8 9] HE ranges from mild forgetfulness/reversed sleep patterns to significant impairment of intellectual function, behaviour (including emotional lability) and reduced levels of consciousness. Commonly these signs and symptoms are categorised by the West Haven criteria (graded I–IV), with grade IV representing a coma.[10] HE is known to be one of the most debilitating symptoms in patients with ESLD, with reported poor quality of life (QoL), substantial economic burden and repeated hospital admissions.[8 9] However, there remains a paucity of data on the degree to which HE impacts up on nutritional intake, sarcopenia and physical function.

The relationship between HE and sarcopenia/poor functional status is likely bidirectional (figure 1). In addition, to the clinically observed effects on dietary compliance and sedentary lifestyle, HE and in particular hyperammonaemia, have direct effects on muscle cell growth. Ammonia has been found to interact with Nuclear factor kappa B (a protein complex that controls cell survival) and in turn promotes myostatin expression, which is a key muscle protein that inhibits muscle growth.[11 12] Sarcopenia has been shown to significantly increase the risk of both minimal (threefold) and overt (twofold) HE.[13] In part, this is likely explained by the fact that muscle is an alternative organ to the liver for ammonia detoxification, via glutamine synthesis from glutamate.[14] In sarcopenic patients when muscle mass diminishes there is reduced ability of the muscle to compensate for hepatic decompensation, contributing to an increased likelihood of hyperammonaemia and HE.[15–17]

Taking all these factors into account, the combination of HE and sarcopenia is the 'perfect storm' for entering a vicious cycle of poor nutritional status/intake, worsening muscle health/physical function and overall clinical deterioration from ESLD. While lactulose and rifaximin remain the mainstay for pharmaceutical management of HE, the only curative treatment for HE and ESLD remains liver transplantation.[18 19] However, understanding the hurdles and importance of nutritional management in patients with HE and its impact on sarcopenia and physical function is essential for optimising the efficacy of nutrition in these challenging cases. Thus, the aim of the current case–control study is to prospectively investigate the impact of HE on nutritional intake and sarcopenia status in patients with ESLD (table 1).

METHODS

Study design overview

The HENS-LIV study is a single-centre, case–control observational prospective 6-week study of 20 outpatients with ESLD in the presence (cases) or absence (controls) of HE, to understand the impact of HE on patients reported nutritional intake (24-hour food recall vs 3-day food diaries) and compliance with dietetic advice/nutritional targets. In parallel, the study will use simple, 'by the bed-side' tests to evaluate the impact of HE and nutritional intake on sarcopenia (MAMC, ultrasound imaging of quadriceps muscle), exercise capacity (DASI), physical function (chair rise, handgrip) and overall physical frailty (LFI). In addition, physical activity will be measured

Table 1 Primary and secondary endpoints

Primary endpoints	1. The impact of HE on energy (kcal) and protein (g) intake compared with those without HE. 2. The impact of HE on measures of Sarcopenia, exercise capacity, physical function and overall physical frailty compared with those without HE.
Secondary endpoints	1. The impact of HE on energy (kcal,) and protein (g) intake reporting compared with those without HE, using 24-hour food recall and 3 day food diary. 2. The impact of HE on changes in energy (kcal) and protein (g) intake, sarcopenia, exercise capacity, physical function and overall physical frailty compared with thise without HE, between baseline (study visit 1) assessment compared with review (study visit 2).

HE, hepatic encephalopathy.

using accelerometery. Recruited patients will undergo assessment of these parameters at baseline and again at 6–8 weeks (in-line with their routine clinical follow-up) to assess for any changes in nutritional intake, nutritional status and sarcopenia/functional status. Standard medical, dietetic and physiotherapy care will continue for all participants as determined by their clinical team, in keeping with current guidelines. The control population will consist of ESLD in the absence of HE in order to benchmark nutritional intake, status and physical parameters in patients who are not neurologically compromised by HE.

Study population

A convenience sample size of 20 eligible patients will be selected from the University Hospitals Birmingham (UHB) tertiary outpatient liver unit. Undertaking clinical research with this patient group is challenging due to the fluctuating nature of a wide spectrum of mental and motor symptoms including poor coordination with higher risk of falls, difficulty concentrating and cognitive impairment. Additionally, with the main research questions being exploratory (ie, how HE may impact on the method of reporting diet/nutritional intake, how HE may impact on compliance with nutrition advice and recommended targets set, and how HE may impact sarcopenia and QoL), it was not deemed appropriate to power the study.[20] However, this may present as a study limitation as the small sample size may risk underpowering the final outcomes, leading to a type II error. Patients will be eligible to be included in the study if they meet the following eligibility criteria:

Inclusion criteria

1. Adults aged ≥18 years.
2. Able to provide written consent to the study, as judged by the clinical investigators.
3. Confirmed diagnosis of decompensated liver cirrhosis.
4. For the HE arm—evidence of overt encephalopathy at time of recruitment (ie, ≥West-Haven 1).
5. For the non-HE arm—no evidence of minimal encephalopathy (ie, normal portosystemic hepatic encephalopaty score (PHES) test and no recorded clinical symptoms of HE in last 3 months).

Exclusion criteria

1. Refusal or lacking ability to be able to provide written informed consent (at baseline visit).
2. Previous history of liver transplantation.
3. Currently enrolled in a registered interventional pharmaceutical trial.
4. Inpatient admission at the time of assessment/baseline clinic visit.
5. Confirmed ESLD but with active alcohol consumption.

Once deemed eligible, patients will be provided with a study participant information sheet. Patients will be contacted by the principal investigator through a telephone call 5–7 days after this information has been sent, to explain the study in detail and to answer questions. If patients are willing to take part, an appointment will be arranged in line with their next hepatology outpatient clinic appointment, when patients will be able to provide informed written consent.

Data collection

Data will be collected at baseline (visit 1) and then at week 6±2 weeks (visit 2) (figure 2). This 6±2 weeks follow-up period is in line with patient's standard-of-care outpatient clinic appointment pattern at the hospital, which the 'UHB Liver Patient and Public Involvement' (PPI) group felt was very important due to the wide geographical area of the quaternary liver unit service catchment area. This timeframe also allows for comparison of changes in nutritional intake (calorie and protein) and the impact on sarcopenia status over time between baseline and follow-up visits.

There are two outpatient liver transplant assessment clinics per week (patients attending n=6–9), which are dedicated to assessing patients for their eligibility to be listed for a liver transplant, and one liver transplant waiting list clinic per week (n=12–24), which is dedicated to patients who are either waiting to be listed for a liver transplant or who are currently listed for a liver transplant. These clinics will provide access to a wide range of participants who have ESLD±HE.

All participants will be provided with a 3-day food diary as part of their routine standard of care and asked to bring this completed to their baseline assessment (visit 1). During study visit 1, baseline assessments will include:

- Twenty-four-hour food recall.

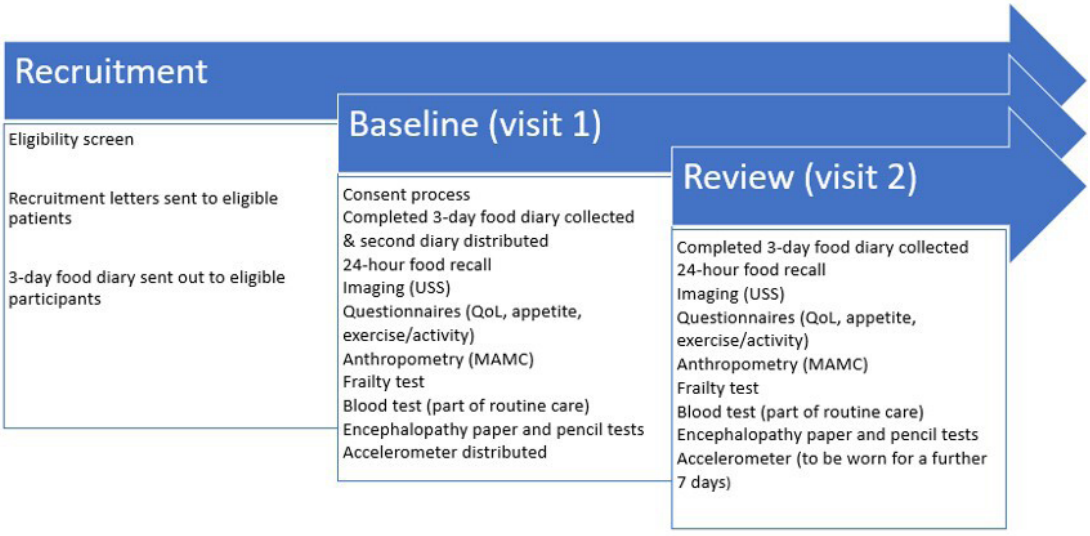

Figure 2 Study design overview. MAMC, mid-arm muscle circumference; QoL, quality of life.

- Sarcopenia (ultrasound imaging of quadriceps muscle group) (SONIMAGE MX1 Portable Ultrasound System, Konica Minolta, Tokyo, Japan),[21] anthropometry).[22 23]
- Muscle strength (handgrip strength (HGS)).[24]
- Physical function (chair rise time).
- Physical activity through wearing an accelerometer for 7 days after each study visit (GENEActiv, UK).
- Physical frailty (LFI).[25]
- Exercise capacity (DASI).[26]
- Qualitative assessment of QoL (36-item Short-Form survey) SF-36v2, (Quality Metric Health Outcomes Solutions, Lincoln, USA).
- Appetite (eight-item Council on Nutrition Appetite Questionnaire and Emotional Appetite Questionnaire questionnaires).[27 28]
- HE severity status (shortened Portosystemic Encephalopathy Syndrome Test).[29]

At the end of this baseline visit, participants will be provided with another 3-day food diary and asked to complete this prior to their follow-up assessment (visit 2). In the event that a participant loses capacity in the 6-week interval period between the clinic visits, a personal consultee of the participant can provide (or withdraw) ongoing consent to act in the participants best interests until they regain capacity. On return to clinic at week 6±2 weeks (visit 2) all of the above will be repeated and the second food diary will be collected. With regard to accelerometery, data will be captured for the 7 days after visit 1 and the first 7 days after visit 2. At study visit 2, all participants will be provided with a stamp-addressed envelope and requested to post the accelerometer back to the research team.[30]

Other data collection (visit 1 and 2)

Measures of encephalopathy severity

- West-Haven Criteria I–IV stage (overt encephalopathy).
- Glasgow Coma Scale—overall conscious level.
- Serum Ammonia as per Birmingham liver unit protocol (A. venous sampling; B. taken at approximately the same time of day for study visit 1 and study visit 2; C. samples instantly transported on ice and processed within 15 min).

Other clinical measures

- UK Model of End-stage Liver Disease.
- Child-Pugh Score (5–15).
- Full blood count.
- Urea and electrolytes.
- Liver function tests (alanine aminotransferase; ALT, aspartate aminotransferase; AST, alkaline phosphatase; ALP, bilirubin, albumin).
- Blood micronutrients (zinc, selenium, copper, vitamin D).
- Myostatin (serum).

Data analysis

All quantitative data will be entered into a purpose-designed access database and exported for statistical analysis into SPSS (V.26). Baseline characteristics will be expressed using descriptive statistics. The Shapiro-Wilk normality test will be used initially, but due to the small sample size non-parametric tests will be applied.

Each 3-day food diary and each 24-hour recall will be analysed using DietPlan (V.7) to primarily identify total daily calorie intake and total daily protein intake. The mean difference of each of these nutrients between patients with and without HE will be tested by Mann-Whitney U test; at different time points. The mean difference between baseline (study visit 1) and follow-up (study visit 2) for each of these nutrients will be tested by Wilcoxon signed-rank test; as will the other patient characteristics and measures of muscle health. In addition, Bland-Altman plots will be used to measure agreement between each paired nutrient.

Non-parametric analysis via Spearman correlation will be used to compare nutritional intake primarily with muscle mass on ultrasound, as well as the other key outcome measures listed including HGS, LFI, DASI and severity of HE.

Patient and public involvement

The Birmingham Liver PPI group meet twice yearly to review recruitment and conduct of studies on the Liver portfolio at UHB. Through this forum, the Birmingham Liver PPI group supported development of the research design, hypothesis and reviewed the final protocol. The results/findings will be presented to the Liver PPI group and in written format to key patient groups including PSC Support group, PBC Foundations, BLTG patient groups and the British liver trust in the form of a lay summary. Study participants who have requested a summarised report of the findings as part of the consent process will be provided with a lay summary also.

Storage of data

Participant identification on the case reports form (CRF) will be through their unique participant study number, which will be allocated at the time of consent into the study. The principal investigator will collect all data for each participant and record this in the CRF. Data will be collected from the time the patient is consented into the study through to the following 7 days after their follow-up (study visit 2) where accelerometery data will continue to be captured. Data from the CRF will be entered into a secure password-protected database held on a UHB Trust computer. All clinical data will be stored as per National Health Service (NHS) regulations. Due care will be taken to ensure data safety and integrity, and compliance with the Data Protection Act 2018. All essential documentation and trial records will be stored in conformance with the applicable regulatory requirements, and access to stored information will be restricted to authorised personnel. Coded research data will be stored for 6 years anonymously under the property of UHB NHS Foundation Trust in keeping with good clinical practice.

Case report form

CRFs will include baseline and follow-up outcome changes for measures of sarcopenia status, muscle function/frailty, physical activity and exercise capacity, 24-hour dietary intake recall and questionnaire scores. Other CRF data incorporated in the electronic database will include medical history and eligibility screening.

Sponsorship, indemnity and monitoring

The UHB will act as the sponsor through the duration of the study. As sponsor, UHB will be responsible for the general conduct of the study and indemnify the study centre against any claims arising from any negligent act or omission by the hospital, in fulfilling the sponsor role in respect to the study.

DISCUSSION

Understanding the impact of HE on patient reported nutritional intake and nutritional and sarcopenia status is an unmet need. Patients with ESLD and HE pose unique challenges in clinical practice, compared with those who are not burdened by HE. Recognised signs and symptoms of HE (including fatigue, daytime somnolence, reverse sleep patterns, forgetfulness, confusion/altered conscious state) collectively may impact on an individual's ability to prepare food, consume food/supplements, comply with nutritional advice, recall/record nutritional intake and in addition significantly affect their physical activity and functional status. The combination of poor nutritional intake, protein catabolism and poor levels of physical activity in particular, increase the risk of sarcopenia and the associated physical frailty.

In recent years, international liver disease associations (including EASL[9] and ESPEN[10]) have set clear guidelines regarding optimal protein intake (eg, 1.5–2.0 g/kg/day) and limiting periods of fasting (eg, night-time snacks) in patients with decompensated ESLD.[10 18] There remains, however, a lack of prospective clinical data investigating the impact of HE on nutritional intake/compliance, in parallel to a robust assessment of muscle health function in patients with ESLD and HE. Several questions remain:

- How does HE impact on the method of recording diet/nutritional intake (24 hours recall vs 3-day food diary)?
  For the purposes of this study, we elected to use the two most common forms of patient food recall/record in order to evaluate if there were discrepancies in data collection and in relationship to the clinical nutritional/physical status.
- How does HE impact on compliance with nutritional advice and target recommendations over a 6-week period?
  By reviewing the patient's food diaries in conjunction with nutritional status, it will provide a unique opportunity to gain insights into how HE (vs non-HE) impacts on nutritional progress/management as an outpatient.
  In turn how does HE and nutritional input impact on muscle mass and physical function.
- How does HE and nutritional status impact on QoL?
  Very little is published on the impact of HE on QoL in ESLD and this may relate to nutritional/functional status.

Although a small-scale study, it is important that the liver community start to understand the impact of HE (in comparison to a non-HE cohort) on nutritional management in order to optimise the management of patients with ESLD and HE in the future. In conjunction with non-pharmaceutical (eg, hydration, avoiding constipation) and pharmaceutical (eg, lactulose and rifaximin, along with avoidance of sedative medications) interventions for HE, it is important to gain a better understanding of the bi-directional relationship between HE and nutrition/muscle health in order to adapt and develop specifically dietetic and exercise models of care for these challenging cases in the future.

The eligibility criteria were specifically determined to exclude inpatient hospital admission at baseline to avoid severe HE (brittle) and those requiring daily medical input. A challenge with prospective studies in HE is the potential the participant will lose capacity to maintain consent during the study. Even though the study duration is short (6 weeks), we will have nominated personal consultees in the study, in keeping with National REC guidelines, in order to act in the participants best interests.

Twitter Jennifer Towey @liver_dietitian

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Contributors JT: concept, design, recruitment, first draft and review/editing of final manuscript. MJA and CG: concept, design, recruitment, first draft and review/editing of final manuscript. CN: recruitment, first draft and review/editing of final manuscript. AH and NR: review/editing of final manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Wales Research Ethics Committee 2 and Health Research Authority (REC reference: 21/WA/0216) Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement This case–control study is still open for data collection, and therefore, data are not yet available.

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REFERENCES

1 Kalafateli M, Konstantakis C, Thomopoulos K, *et al*. Impact of muscle wasting on survival in patients with liver cirrhosis. *World J Gastroenterol* 2015;21:7357–61.
2 Dasarathy S. Cause and management of muscle wasting in chronic liver disease. *Curr Opin Gastroenterol* 2016;32:159–65.
3 Ebadi M, Bhanji RA, Mazurak VC, *et al*. Sarcopenia in cirrhosis: from pathogenesis to interventions. *J Gastroenterol* 2019;54:845–59.
4 Lai JC, Dodge JL, Sen S, *et al*. Functional decline in patients with cirrhosis awaiting liver transplantation: results from the functional assessment in liver transplantation (FrAILT) study. *Hepatology* 2016;63:574–80.
5 Montano-Loza AJ, Meza-Junco J, Prado CMM, *et al*. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2012;10:166–73.
6 Lai JC, Rahimi RS, Verna EC, *et al*. Frailty associated with Waitlist mortality independent of ascites and hepatic encephalopathy in a multicenter study. *Gastroenterology* 2019;156:1675–82.
7 Tandon P, Ney M, Irwin I, *et al*. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl* 2012;18:1209–16.
8 , American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European association for the study of the liver and the American association for the study of liver diseases. *J Hepatol* 2014;61:642–59.
9 European Association for the Study of the Liver, Montagnese S, Rautou PE, Romero-Gomez M. EASL clinical practice guidelines on the management of hepatic encephalopathy. *J Hepatol* 2022;77:807–24.
10 Vilstrup H, Amodio P, Bajaj J, *et al*. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American association for the study of liver diseases and the European association for the study of the liver. *Hepatology* 2014;60:715–35.
11 Carnac G, Vernus B, Bonnieu A. Myostatin in the pathophysiology of skeletal muscle. *Curr Genomics* 2007;8:415–22.
12 Qiu J, Thapaliya S, Runkana A, *et al*. Hyperammonemia in cirrhosis induces transcriptional regulation of myostatin by an NF-κB-mediated mechanism. *Proc Natl Acad Sci U S A* 2013;110:18162–7.
13 Wijarnpreecha K, Werlang M, Panjawatanan P, *et al*. Association between sarcopenia and hepatic encephalopathy: a systematic review and meta-analysis. *Ann Hepatol* 2020;19:245–50.
14 Chen H-W, Dunn MA. Muscle at risk: the multiple impacts of ammonia on sarcopenia and frailty in cirrhosis. *Clin Transl Gastroenterol* 2016;7:e170–3.
15 Ciećko-Michalska I, Szczepanek M, Słowik A, *et al*. Pathogenesis of hepatic encephalopathy. *Gastroenterol Res Pract* 2012;2012:1–7.
16 Merli M, Giusto M, Lucidi C, *et al*. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. *Metab Brain Dis* 2013;28:281–4.
17 Lucero C, Verna EC. The role of sarcopenia and frailty in hepatic encephalopathy management. *Clin Liver Dis* 2015;19:507–28.
18 Plauth M, Cabré E, Campillo B, *et al*. ESPEN guidelines on parenteral nutrition: hepatology. *Clin Nutr* 2009;28:436–44.
19 Flamm SL. Rifaximin treatment for reduction of risk of overt hepatic encephalopathy recurrence. *Therap Adv Gastroenterol* 2011;4:199–206.
20 Whitehead AL, Julious SA, Cooper CL, *et al*. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res* 2016;25:1057–73.
21 Hari A, Berzigotti A, Štabuc B, *et al*. Muscle psoas indices measured by ultrasound in cirrhosis - Preliminary evaluation of sarcopenia assessment and prediction of liver decompensation and mortality. *Dig Liver Dis* 2019;51:1502–7.
22 Elia M. The 'MUST' report: nutritional screening in adults: A Multidisciplinary responsibility. Development and use of the 'Malnutrition Universal Screening Tool' ('MUST') for adults. A report by the Malnutrition Advisory Group for the British Association of Parental and Enteral Nutrition (BAPEN) 2003.
23 Norton K, Olds T. *Anthropometrica*. Sydney: Australia University of New South Wales Press, 2000.
24 Daphnee DK, John S, Vaidya A, *et al*. Hand grip strength: a reliable, reproducible, cost-effective tool to assess the nutritional status and outcomes of cirrhotics awaiting liver transplant. *Clin Nutr ESPEN* 2017;19:49–53.
25 Lai JC, Covinsky KE, Dodge JL, *et al*. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017;66:564–74.
26 Hlatky MA, Boineau RE, Higginbotham MB, *et al*. A brief self-administered questionnaire to determine functional capacity (the Duke activity status index). *Am J Cardiol* 1989;64:651–4.
27 Wilson M-MG, Thomas DR, Rubenstein LZ, *et al*. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *Am J Clin Nutr* 2005;82:1074–81.
28 Nolan LJ, Halperin LB, Geliebter A. Emotional appetite questionnaire. construct validity and relationship with BMI. *Appetite* 2010;54:314–9.
29 Nabi E, Bajaj JS, Jasmohan B. Useful tests for hepatic encephalopathy in clinical practice. *Curr Gastroenterol Rep* 2014;16:362.
30 Van Remoortel H, Giavedoni S, Raste Y, *et al*. Validity of activity monitors in health and chronic disease: a systematic review. *Int J Behav Nutr Phys Act* 2012;9:1–23.