From Department of medicine, Huddinge
Karolinska Institutet, Stockholm, Sweden

ASSESSMENT AND PROGNOSTIC IMPORTANCE OF NUTRITIONAL STATUS AND BODY COMPOSITION IN LIVER TRANSPLANTATION

Catarina Lindqvist

Karolinska Institutet

Stockholm 2020

المنارة للاستشارات
ww

All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet.
Printed by Arkitektkopia AB, 2020
© Catarina Lindqvist, 2020
ISBN 978-91-7831-658-8

المنارة للاستشارات

ww

Assessment and prognostic importance of nutritional status and body composition in liver transplantation

THESIS FOR DOCTORAL DEGREE (Ph.D.)

For the degree of Ph.D. at Karolinska Institutet the thesis is defended in lecture hall Erna Möller, Karolinska Institutet, Blickagången 16, Flemingsberg

Friday, October 9th 2020 at 09.00

By

Catarina Lindqvist

Principal Supervisor:

Associate Professor Staffan Wahlin
Karolinska Institutet
Department of Medicine, Huddinge

Co-supervisors:

Doctor of Medicine Ammar Majeed
Monash University, Melbourne, Australia
Department of Central Clinical School

Associate Professor Frode Slinde
University of Gothenburg
Department of Food and Nutrition, and Sport Science

Opponent:

Professor Mathias Plauth
Municipal Hospital of Dessau, Dessau, Germany
Department of Internal Medicine

Examination Board:

Professor Marie Löf
Linköping University
Department of Health, Medicine and Caring Sciences
Senior researcher
Karolinska Institutet
Department of Biosciences and Nutrition

Professor Stergios Kechagias
Linköping University
Department of Medical and Health Sciences

Associate Professor Gustaf Herlenius
Gothenburg University
Institute of Clinical Sciences

Stockholm 2020

المنارة للاستشارات

ww

المنارة للاستشارات

To my patients, I hope I can improve your care.

المنارة للاستشارات

ww

المنارة للاستشارات

ABSTRACT

Chronic liver disease and liver cirrhosis are progressive diseases closely linked to metabolism and nutritional status. Weight loss is a result of negative energy balance and is therefore a good measure of risk of malnutrition. Screening and assessment of malnutrition in patients with liver cirrhosis is difficult because ascites and oedema are prevalent in late stages of liver cirrhosis. Accumulated fluid could make weight loss as an indicator of malnutrition inappropriate and malnourishment in obese patients can be challenging to identify. Knowledge about body composition, especially the presence of sarcopenia or sarcopenic obesity, is of great clinical value in the liver transplant setting. The scientific and clinical field is hampered by a lack of consensus on how to assess nutritional status in patients with liver cirrhosis. More research is needed to clarify the first part of the nutrition care process: nutritional assessment.

The aims of this thesis were to extend knowledge about nutritional assessment for patients with chronic liver disease before and after liver transplantation. The different parts of the nutritional assessment that are studied in my thesis are body composition methods, nutrition impact symptoms (NIS) and estimation of energy needs.

Study I and Study II were retrospective cohort studies based on patients that underwent liver transplantation between 2009-2012. *Study III* was a prospective cross-sectional study of patients undergoing evaluation for liver transplantation between 2016-2018. *Study IV* was based on a retrospective analysis of the early phase post liver transplantation for patients who underwent a liver transplantation between 2011-2018. Information on body composition was retrieved from dual-energy x-ray absorptiometry (DXA) scans and computed tomography (CT) scans together with anthropometric data, as well as data from questionnaires and information from indirect calorimetry. Additionally, information was obtained from medical charts and the local liver transplant register.

In *study I*, the influence of nutritional status on outcome after liver transplantation was studied. The prevalence of malnutrition was 2-20 % during the pre-transplant evaluation. The prevalence differed between genders and assessment methods. When measured with DXA, 20 % of the men and 5 % of the women were malnourished. An association was found between fat-free mass index and occurrence of infections within 30 days after the liver transplantation. In *study II* we performed inter-method comparisons between muscle mass depletion measured with DXA and CT. Muscle mass depletion was found in 30-40% of the entire population, in women it varied between 13-69% with the different methods and in men between 27-40%. Muscles in arms and legs measured with DXA had a strong correlation

المنارة للاستشارات

ww

with muscles at the third lumbar vertebrae (L3) measured with CT but whole-body fat-free mass measured with DXA did not. In *study III* the aim was to assess the prevalence and severity of NIS and to explore associations with malnutrition and health-related quality of life (HRQOL). The prevalence of malnutrition was 32%. NIS were prevalent with 90% of the population presenting with one symptom or more and 51% of the population with four or more symptoms. A higher frequency of NIS was associated with malnutrition and worse HRQOL. Energy requirement early after liver transplantation was studied in *study IV*, and we found that the Harris & Benedict equation for predicting resting energy expenditure (REE), as well as the fixed factors 25, 30, 35 kcal/kg suggested in European guidelines, provided estimates of energy requirement that were too inaccurate to be of clinical value. There is a risk of both under- and overfeeding individual patients if fixed factors are used to estimate energy requirement early after liver transplantation. Measured REE was significantly associated ($p < 0.05$) with age, gender, Model for End-Stage Liver Disease score before liver transplantation, surgery time and graft cold ischemia time.

Together, the results from this thesis contributes to an understanding of the importance of a structured nutritional assessment as well as body composition assessment in patients undergoing liver transplantation. The proportion of individuals who are malnourished or muscle mass depleted varies depending on the method used, NIS are prevalent and associated with malnutrition and worse health-related quality of life. Energy requirements should be measured and not estimated after liver transplantation.

المنارة للاستشارات

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers which are referred to in the text by their Roman numerical:

I. **Lindqvist C**, Majeed A, Wahlin S. Body composition assessed by dual-energy X-ray absorptiometry predicts early infectious complications after liver transplantation. *Journal of Human Nutrition and Dietetics*, 2017, 30 (3), 284-291. doi: 10.1111/jhn.12417

II. **Lindqvist C,** Brismar T, Majeed A, Wahlin S. Assessment of muscle mass depletion in chronic liver disease; dual-energy x-ray absorptiometry compared with computed tomography. *Nutrition*, 2019, 61, 93-98. doi: 10.1016/j.nut.2018.10.031

III. **Lindqvist C**, Slinde F, Majeed A, Bottai M, Wahlin S. Nutrition impact symptoms are related to malnutrition and quality of life – A cross-sectional study of patients with chronic liver disease. *Clinical Nutrition*, 2019. doi.org/10.1016/j.clnu.2019.07.024

IV. **Lindqvist C**, Nordstedt P, Nowak G, Slinde F, Majeed A, Bottai M, Wahlin S. Energy expenditure early after liver transplantation: better measured than predicted. *Nutrition*, 2020, 79-80:110817. doi: 10.1016/j.nut.2020.110817.

المنارة للاستشارات

CONTENTS

المنارة للاستشارات

ww

المنارة للاستشارات
ww

LIST OF ABBREVIATIONS

ASMI	Appendicular skeletal muscle mass index
BIA	Bioimpedance analysis
BMI	Body mass index
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
EASL	The European Association for the Study of Liver Disease
ESPEN	The European Society for Clinical Nutrition and Metabolism
EWGSOP	The European Working Group on Sarcopenia in Older People
FMI	Fat mass index
FFMI	Fat-free mass index
GLIM	The Global Leadership Initiative on Malnutrition
HB	Harris & Benedict equation
HCC	Hepatocellular carcinoma
HGS	Hand-grip strength
HRQOL	Health-related quality of life
IC	Indirect calorimetry
L3	Third lumbar vertebrae
LOS	Length of stay
MAC	Mid-arm circumference
MAMC	Mid-arm muscle circumference
MELD	Model for end stage liver disease
MRI	Magnetic resonance imaging
NIS	Nutrition impact symptoms
PSC	Primary sclerosing cholangitis
REE	Resting energy expenditure
SGA	Subjective global assessment
SMI	Skeletal muscle mass index
TSF	Triceps skinfold

المنارة للاستشارات
ww

1 PREFACE

As a registered dietitian, I started working at the Hepatology and Liver Transplantation Clinics in 2009, one year after I became a registered dietitian. Working with patients with chronic liver disease was difficult when I had little experience of the patient group. As a clinical dietitian I struggled with the nutritional assessment of the patients with ascites and oedema. After some years working in the liver team, it was obvious for my clinical eye when a patient needed nutritional support. However, it was not always possible to diagnose malnutrition when applying the common assessment factors weight, weight loss and low BMI. Even if my clinical experience told me that I needed to intervene, I did not have good ways to evaluate if the treatment was effective. All the things I learned in school seemed insufficient and I was frustrated of the lack of tools in the everyday clinic to assess my patients.

All health professionals want to improve the care for their patients, and as a dietitian it is essential to perform a nutritional assessment before implementing nutritional interventions. I realised that the way to go if I wanted to be a better clinician was to go into research and explore new methods to perform nutritional assessment. This thesis is built on four studies putting together three of my main clinical frustrations: how do I assess malnutrition in patients suffering from chronic liver disease, which symptoms affecting the patients ability to eat are important to treat and how much energy do the patients really need after a liver transplantation?

المنارة للاستشارات

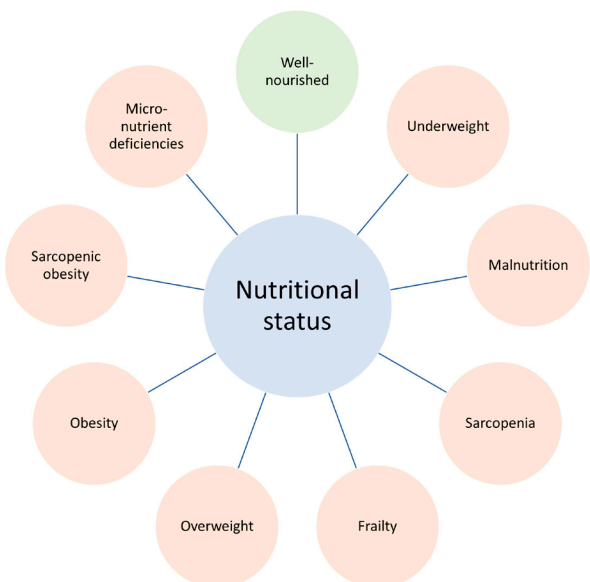
ww

2 INTRODUCTION

2.1 Nutritional status

There are more than 3 million hits on Google Scholar and 60 000 on PubMed for the phrase nutritional status. The phrase nutritional status can encompass different meanings. The MeSH term database defines it as *"State of the body in relation to the consumption and utilisation of nutrients"*. In this thesis, the phrase nutritional status refers to the state of the body, e.g. whether the individual is well-nourished, malnourished, obese, or underweight (Figure 1). The nutritional status can also refer to lack of micronutrients which is important but falls beyond the scope of this thesis. Nutritional assessment is the first part of the Nutrition Care Process (1). It is a systematic process of collecting and interpreting information about an individual's nutrient intake, clinical signs, lifestyle, medical history and anthropometry. With this information it is possible to evaluate the nutritional status which then guides the nutritional interventions. Assessment of nutritional status can be a complex procedure. All methods are to some extent approximations and the validity and reliability of the method needs to be considered as well as what reference data the results are compared with. Nutritional assessment in patients with liver cirrhosis is especially challenging because of the common problem with fluid accumulation. This thesis explores different methods to perform nutritional assessment in patients undergoing liver transplant evaluations and liver transplantation.

Figure 1. Aspects of nutritional status in patients with chronic liver disease



المنارة للاستشارات
ww

2.1.1 Malnutrition

Malnutrition can refer to either undernutrition or overnutrition; in this thesis it is used as a synonym for undernutrition. In Europe, 20 million individuals are at risk of malnutrition and the cost for the society is estimated to be around 120 Billion Euros annually (2). Malnutrition increases both morbidity and mortality, and results in a functional impairment and lower quality of life (3-5). Malnutrition is recognised as part of the clinical symptoms of chronic liver disease, however there are many ways to measure it. One of the most common ways to diagnose malnutrition, The Subjective Global Assessment of Nutritional status (SGA) was introduced in 1987 by Detsky et al (6). SGA includes a technique built on patient history and a physical examination and has been thoroughly used in different studies investigating nutritional status in patients with liver cirrhosis (7-9). SGA and the liver-specific Royal Free Hospital-Global Assessment (RFH-GA) (10) are examples of bedside nutritional assessment techniques. Examples of single measure nutritional assessment techniques are mid-arm muscle circumference (MAMC) and hand grip strength (HGS). In the last two decades advanced methods have become more available to measure body composition such as bioelectrical impedance analysis (BIA), dual-energy x-ray absorptiometry (DXA) and cross-sectional imaging assessment via computed tomography (CT) or magnetic resonance imaging (MRI). A recent systematic review of 47 studies of patients with liver cirrhosis before and after liver transplantation found 32 different definitions for malnutrition (11). The prevalence of malnutrition in patients with liver cirrhosis is highly dependent on assessment method as well as severity of the liver disease, and reported frequencies of malnutrition vary between 5-99% (12).

During the last decade major nutrition organisations have proposed different definitions of malnutrition. The European Society for Clinical Nutrition and Metabolism (ESPEN) describe malnutrition as *"a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease"* (13). Malnutrition has different origins, and according to ESPEN, there are several subgroups of malnutrition. Malnutrition can be disease-related with or without an inflammatory process or it can be hunger-related (13).

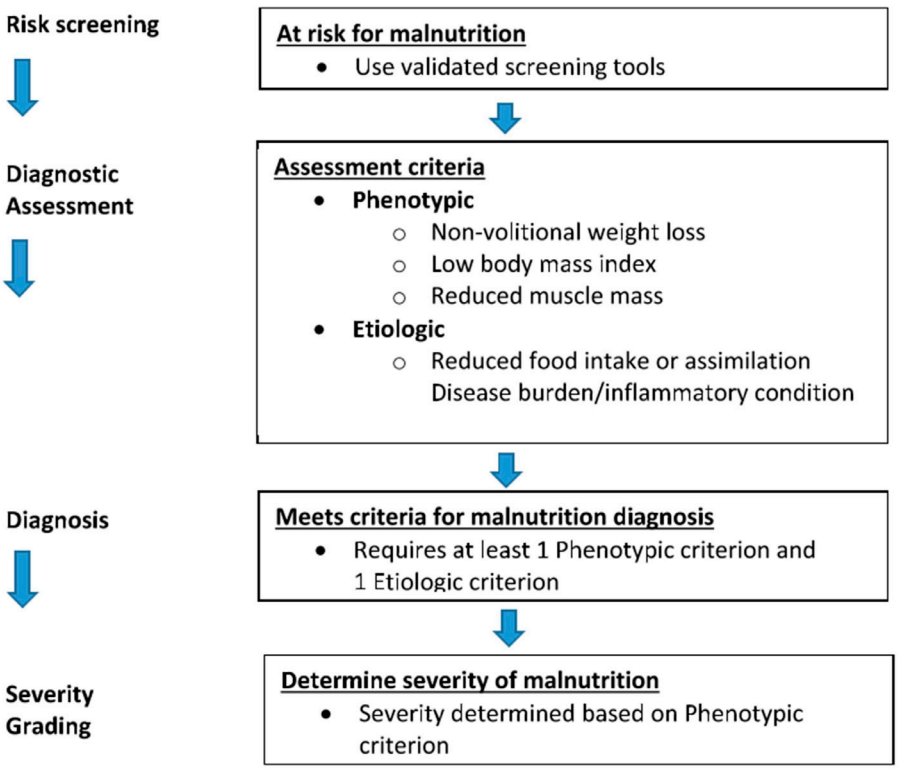
Throughout the years, many different criteria on how to diagnose malnutrition have been suggested. The American Society for Parenteral and Enteral Nutrition (ASPEN) and The Academy for Nutrition and Dietetics published a consensus statement in 2012 suggesting that no single parameter is definitive for malnutrition in adults (14). Two or more of the following six characteristics should be present to diagnose malnutrition: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localised or generalised fluid accumulation that may sometimes mask weight loss and diminished functional status as measured

المنارة للاستشارات

ww

by hand-grip strength. The most recent criterion was suggested by The Global Leadership Initiative on Malnutrition (GLIM) who published a consensus report from the global clinical nutrition community in 2018 (15), where both a phenotypic and a etiologic criterion need to be present to diagnose malnutrition (Figure 2). The phenotypic criterium involves non-volitional weight loss, low body mass index or reduced muscle mass. The etiological criteria are reduced food intake or assimilation, inflammation or disease burden.

Figure 2. GLIM diagnostic scheme for screening, assessment, diagnosis and grading of malnutrition.



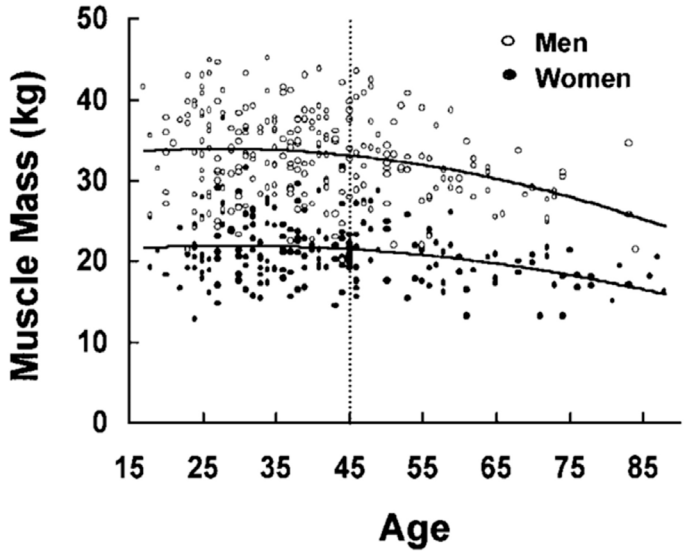
From Cederholm et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community Clin Nutrition. 2019 Feb;38(1):1-9. Doi: 10.1016/j.clnu.2018.08.002. Reprinted with permission.

المنارة للاستشارات
ww

2.1.2 Sarcopenia and muscle mass depletion

Sarcopenia was originally a term used to describe the loss of muscle mass during normal ageing. Sarcopenia can be defined as: "*a syndrome of its own characterised by the progressive and generalised loss of skeletal muscle mass, strength and function (performance) with a consequent risk of adverse outcomes"*(13). The amount of skeletal muscle mass is influenced by both age and gender. In healthy adult individuals, the skeletal muscle mass is relatively stable, and after the age of ~45 years skeletal muscle mass starts to progressive decline (16) (Figure 3).

Figure 3. The relationship between skeletal muscle mass and age.



From Janssen et al, Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr, J Appl Physiol (1985). 2000 Jul;89(1):81-8 (16). Reprinted with permission.

Primary sarcopenia is the term suggested for age-related loss of muscle mass while secondary sarcopenia can appear secondary to a systemic disease such as organ failure or malignancy (17). Secondary sarcopenia can appear in all ages. The causes of sarcopenia are multifactorial and can be a combination of aging, disease, inactivity and malnutrition. The European Working Group on Sarcopenia in Older People (EWGSOP) first recommendation on how to diagnose sarcopenia put low muscle mass as a mandatory criteria for the diagnose (18). The sarcopenia diagnose is confirmed if low muscle mass is found in combination with either low muscle strength or low physical performance. In a review of 50 articles of the relationship between body composition, muscle strength and functional decline in older people, muscle strength and obesity were associated with functional decline

المنارة للاستشارات
ww

but low muscle mass was not (19). The recently updated recommendations from EWGSOP on how to diagnose sarcopenia (17) emphasise the importance of declining muscle function. In the updated diagnostic scheme to diagnose sarcopenia, the first step is to measure muscle strength. If muscle strength is low, the next step is to measure if muscle quantity or quality is low. If these two criteria are met the sarcopenia diagnosis is confirmed. After that, physical performance should be tested. Sarcopenia is considered severe if a person has low muscle strength, low muscle quantity or quality and low physical performance. It can be difficult to identify whether sarcopenia is primary or secondary. In this thesis the term sarcopenia incorporates both primary and secondary sarcopenia. Sarcopenic obesity is the combination of loss of skeletal muscle mass and obesity. It should be noted that several studies performed on patients with liver cirrhosis use the term sarcopenia for patients with low muscle mass but without any measurement of muscle strength or physical performance (20-23).

Muscle mass depletion describes the depletion of muscle mass compared to a reference population. The determinants of muscle mass in healthy subjects are age, gender, body region and fat mass (24)**.** Measures of skeletal muscle mass should be normalised for height, and ethnicity-specific cut-offs are recommended (24). Because of the decreasing amount of muscle mass with age, it can be advantageous to use age-specific reference values when presenting how many individuals in a population is suffering from low amount of muscle mass.

Both sarcopenia and frailty are acknowledged as important determinants for waiting list mortality (25, 26) in the liver transplant candidate. Frailty is a state of vulnerability and limited reserve capacity. This leads to reduced capability to withstand acute decompensating events and therefore frailty is a risk factor for dependence and disability. In liver transplantation candidates, the concept of physical frailty includes functional performance, functional capacity, and disability (27). In the studies included in this thesis neither sarcopenia nor frailty was evaluated because of the lack of data on muscle strength and physical performance in the majority of the study populations.

2.1.3 Adipopenia

The body has two main energy reserves, fat and muscles, that can be used in lack of energy from nutrient intake. Fat mass constitutes adipose tissue as well as fat in other parts of the body such as in the liver (28). Adipopenia is the depletion of adipose tissue. Visceral and subcutaneous tissues constitute the adipose tissue (29) and can be measured separately with imaging techniques (28), while DXA measures the entire fat mass in the body. In cirrhosis research, sarcopenia has been thoroughly explored in the last decade however adipopenia have not received a

المنارة للاستشارات

lot of attention. Adipopenia is more frequent in females while muscle loss is more characteristic for male patients with liver cirrhosis (30, 31). The cause for these gender disparities in body composition is not fully understood. Ebadi et al found low subcutaneous adiposity to increase mortality risk in females with liver cirrhosis, even after adjusting for Model for End-Stage Liver Disease (MELD) score, but low skeletal muscle index did not (32). In compensated patients, lower visceral adipose tissue index was associated with 12-month decompensation in both male and female patients (33). Adipopenia can be highly relevant for female patients with liver cirrhosis and needs further exploration in future studies.

2.2 Nutritional assessment

2.2.1 Methods for body composition measurement

In the clinical setting, bedside anthropometric measurements such as body mass index (BMI), mid-arm circumference (MAC) and triceps skinfold thickness (TSF) are common and easy to use. BMI is a mathematical formula indicating over or underweight, but it provides no further insight into actual quantities of muscle mass or fat mass. Anthropometric measurements, such as MAMC, which is calculated from MAC and TSF, are time-efficient and the cheapest way to measure body composition. However, the reproducibility of TSF measurement is low because the accuracy depends on the investigators skill (34).

BIA, DXA, CT and MRI are more technically advanced alternatives to measure body composition. There are also more complex methods such as underwater densitometry, air displacement plethysmography and isotope dilution but those are methods mainly used for research. Standardised measurements of central muscle mass by CT or MRI have in recent studies shown potential value, but cost-effective alternatives are needed. DXA is a less expensive alternative that involves minimal radiation exposure. Assessment of muscle mass with CT, and to some extent also with DXA, has attracted much interest in recent years in patients with chronic liver disease (35-38). New clinical practice guidelines for nutrition in chronic liver disease by The European association for the Study of the Liver (EASL) were first presented in April 2018 (39). The guidelines recommend assessment of muscle mass with either CT or with DXA, but do not give any advice about whether the different methods provide comparable results when patients are assessed, or on how to compare outcomes in different studies. An overview of each of the measurement methods advantages and disadvantages is presented in Table 1.

المنارة للاستشارات

ww

Table 1. Nutritional assessment methods of anthropometry, body composition and muscle function

Nutritional assessment method	Strengths	Drawbacks
Body weight Weight change BMI	Low cost Simple to perform Easy to reproduce	Influenced by body fluid changes Cannot identify obese patients at risk for malnutrition
Anthropometric measurements; triceps skin fold measurement, upper arm muscle circumference	Low cost Bedside methods	Influenced by body fluid changes Low interrater reliability Low specificity and low sensitivity
Functional tests: handgrip strength, sit-to-stand test, 6-minute walk	Provides insight into level of frailty	Can be affected by underlying disease or comorbidities Not a direct measure of nutrition
DXA	High precision and accuracy Can measure body composition for both the whole body and parts of the body (40). Differentiates between FM, FFM and bone Safe	Not a bedside method Cannot be used for very tall or severely obese patients Changes in the body's amount of water appears as a change in the amount of lean body mass in repeated measures (41). Differences in software between manufacturers
CT/MRI	Can determine tissue quality High precision Can identify sarcopenic obesity	Needs special software to quantify body composition Often studies a single slice at L3 and extrapolates to whole-body, risk of over/underestimating muscles Radiation exposure
BIA	Can be used bedside Can be portable Non-invasive Inexpensive compared to DXA/CT/MRI	Influenced by body fluid changes Equation not validated for liver cirrhosis population
Air displacement plethysmography	Good reliability and validity Non-invasive	Expensive equipment and not available in most centres Limited literature in cirrhosis
Dilution techniques	Can quantify total body water	Expensive equipment and not available in most centres Time-consuming

Adapted from Di Sebastiano et al (42). BMI; body mass index, DXA; dual-energy x-ray absorptiometry, FM; fat mass, FFM; fat-free mass, CT; computed tomography, MRI; magnetic resonance imaging, BIA; bioimpedance analysis

المنارة للاستشارات
ww

Different components of the body tissues are measured in body composition analysis. Two-component models divide the body into fat mass (FM) and fat-free mass (FFM) while multi-component models divide the body into three or more components (43). In the two-component model, equations are used to estimate the percentage of body fat from the body's density. These equations assume that the density of FFM is 1.1 g/cm³ and the density of FM is 0.9 g/cm³. A potential consequence of using equations is a systematic over or underestimation of body components (44). Multicomponent models take into account individual variations in amount of fluid or the amount of minerals in the FFM (43). Therefore, multi-component models generally provide more accurate estimates than two-component models. The four-component model (body weight, body volume, total body water and bone minerals) is considered most accurate for determining body composition (45) but it requires methods such as densitometry and isotope dilution techniques that are only available in certain centres and these methods are not used in clinical practice.

2.2.2 Dual-energy x-ray absorptiometry

DXA separates the tissue into three compartments: bone mineral, lean soft tissue and fat mass. FFM constitutes of water, protein, glycogen, soft tissue minerals, and bone minerals. The lean soft tissue is the difference between FFM and bone minerals (46). DXA can measure body composition of the whole body but also of different regions of the body (40). During a DXA-measurement two X-rays with different levels of energy are sent through the body. DXA measures the ratio of photon attenuation at the two designated main energies. The X-rays will be weakened to different degrees depending on what kind of tissue the beams are hitting, and the information is then used to calculate body composition. DXA has a good precision, around 1-2 % (47) and reproducibility of FM is approximately 1 % in adult patients. The radiation dose required for a whole-body measurement using DXA is 5-7 μSv (48). Different DXA machines use different techniques, either fan-beam or pencil-beam. A fan-beam corrects for the beam magnification. The main downside of DXA when it comes to liver disease is that it misclassifies changes in the fluid status as a change in lean body mass (41).

2.2.3 Computed tomography

CT as a method to measure body composition was developed around 40 years ago and was presented as a promising method in 1995 (49). Different tissues generate different attenuations when the X-rays pass through tissues, expressed as attenuation relative to air and water. Air is defined as -1000 Hounsfield units (HU) and water as 0 HU. At the image reconstruction at CT imaging each of the image pixels is assigned a HU. The obtained HUs of the imaged tissue can at image processing be used to determine the body composition.

المنارة للاستشارات

ww

The use of CT to measure body composition started to be used more wide-spread in clinical cancer research in 2008 (50) and the first study in patients with liver cirrhosis was published in 2010 (51). During the last nine years more than 75 studies have been published using CT to quantify muscle mass in patients with cirrhosis. Even if the method has attracted a lot of interest in the research community there is still no established methodology which is uniformly used. A variety of techniques is in use, including different software programs, thresholds, slice thicknesses, and tube voltage. Many studies use CT scans performed for clinical reasons and there is a discrepancy in whether contrast-enhanced scans or unenhanced scans are included, and different phases of the scans have been used. Also, different muscles are measured. For example, in some studies the axial and the transversal psoas-muscle are quantified, and other studies measure all spinal and paraspinal muscles. There is also heterogeneity in which cut-offs for low skeletal muscle mass are used. Published cut-offs are based on different types of populations: patients with end-stage liver disease (20) and those with cancer (52).

2.2.4 Energy requirement

Estimating or measuring energy requirement is an important part of the nutritional assessment. Prediction equations (e.g. Harris & Benedict equation) or fixed factors (e.g. 30 kcal per kilogram body weight) is often used to estimate energy requirement in the clinical setting. Resting energy expenditure (REE) can be measured with indirect calorimetry (IC). Energy in the form of carbohydrate and fat provide the body cells with fuel for vital functions and forms heat, water and carbon dioxide. The body's waste products from metabolism, carbon dioxide and water, are removed via the exhaled air. IC measures energy metabolism and uses a technique in which energy metabolism at rest is calculated by measuring the consumption of oxygen and carbon dioxide production by analysis of the exhaled air (53). REE is the sum of organ and tissue metabolic rates (54). To calculate total energy expenditure (TEE) a physical activity level (PAL) is added to REE.

After liver transplantation, some patients have an altered metabolism, often a hyper metabolism (55, 56). To calculate energy requirement based on body weight or prediction equations can therefore be misleading. Previous guidelines recommended using the Harris & Benedict equation (HB) for calculating REE in patients with liver cirrhosis (57). HB was originally developed in 1918. A revision in 1984 confirmed its accuracy in healthy people with a precision of +/- 14 % but HB is unreliable in malnourished patients (58). Different fixed factors (25, 30 and 35 kcal/kg body weight) to calculate energy requirements after liver transplantation have been suggested in recent guidelines from ESPEN and EASL (39, 59, 60).

المنارة للاستشارات
ww

2.2.5 Nutrition impact symptoms

A crucial part of the nutritional assessment is identifying barriers for eating. Disease-related decrease in dietary intake can be attributed to a disturbance of appetite control and a variety of symptoms such as nausea, vomiting, diarrhoea, constipation, depression, anxiety or pain. Aggregated together, these symptoms are called nutrition impact symptoms (NIS) (61). NIS can potentially lead to reduced food intake and thereby contribute to weight loss and risk of malnutrition. Several studies have described how patients with liver diseases suffer from symptoms that affect the ability to eat such as reduced appetite, nausea and early satiety (62-64). How much these symptoms affect nutritional status or quality of life in patients under evaluation for liver transplantation has not been previously studied.

The prevalence of NIS has been studied in patients with cancer, unique individual symptom profiles are suggested to require specific intervention to improve nutritional status (65). NIS such as loss of appetite, difficulty in chewing, dry mouth, thick saliva and pain were associated with decreased food intake (65). One study found that NIS led to reduced energy intake and weight loss (61). In another study, 79% had some symptoms that resulted in eating difficulties one month after start of chemotherapy and the incidence of NIS was associated with a lower quality of life and a poorer performance status (66). Omlin et al. examined NIS with a 12-item NIS checklist and found that 29% had one symptom or more, 21% had two symptoms and 13% had three or more symptoms (67).

In a recent study on patients with gastroenterological and liver diseases, specific NIS such as difficulties swallowing, poor appetite, early satiety and food tasting bad were found to be correlated with low hand grip strength and weight loss (68). NIS have also been investigated in patients with renal disease were NIS was related to nutritional status and mortality (69). NIS is common in patients with chronic obstructive pulmonary disease and malnourished patients have more NIS (70). NIS have not been thoroughly investigated in healthy subjects. Some studies on prevalence of different symptoms, mainly gastrointestinal symptoms, exists with data from the general Swedish population. In a study of 268 randomly selected adults, with the aim to investigate bowel habits, bloating, straining, urgency, and feelings of incomplete evacuation were common findings among both females and males (71). In a study with the aim to establish population-based data to use as a reference from results on studies with patients with head and neck cancer, the prevalence of symptoms of nausea/vomiting was 3.5%, pain 16.6%, appetite loos 5.1%, diarrhoea 5.8% and constipation 5.2%. in a random sample of the Swedish adult population (72).

المنارة للاستشارات

ww

2.3 Liver cirrhosis

Chronic liver disease involves a wide spectrum of different diseases that can result in chronic liver injury. There are toxic diseases such as alcoholic liver disease, autoimmune diseases like autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis (PSC), or viral diseases such as hepatitis B and C or metabolic disorder caused by fat accumulation such as non-alcoholic fatty liver disease.

Liver cirrhosis is the last stage of chronic liver disease that develops when scar tissue, fibrosis, replaces normal, healthy tissue in the liver. Liver cirrhosis is initially asymptomatic (compensated). As the disease progresses, different complications such as portal hypertension, oesophageal varices, ascites, hepatic encephalopathy and hepatorenal syndrome arise (decompensated) (73). For patients with compensated cirrhosis, one-year mortality is approximately 5.4% compared to 20.2% for those with decompensated liver cirrhosis (74). In Sweden, the age-standardised death rate for liver cirrhosis is 4.9 per 100 000 deaths in 2010 and about 0.1% of the European population suffers from cirrhosis (75). The Child-Pugh scoring system is one way to predict mortality (76). The Child-Pugh score has three stages A, B and C where C is the most severe disease. Another score is MELD which can range between 6 to 40, where a higher score indicate a higher mortality risk (77). The populations in the studies in this thesis include patients with chronic liver disease and the majority has liver cirrhosis. The phrase "chronic liver disease" encompasses all stages of liver disease except acute liver failure and the phrase "liver cirrhosis" is specific for when cirrhosis has developed.

2.4 Liver transplantation

Liver transplantation is a standard clinical treatment for patients with many types of liver diseases and liver transplantation is the only life-saving treatment for patients with severe liver disease. The main indications for liver transplantation in Europe are liver cirrhosis, primary liver tumors, cholestatic liver disease and acute liver failure (78). In this thesis no patients with acute liver failure are included.

Before a transplantation is considered, all other meaningful treatment options should be explored. The timing of the decision to transplant involves weighing risk scenarios against each other. Decompensated liver cirrhosis is the most common indication for liver transplantation but other symptoms such as severe fatigue, malnutrition, sarcopenia and severe pruritus are important in the assessment and can be considered indications for liver transplantation. A liver transplantation evaluation is initiated when a patient's health status is deemed to have no chance of improvement and the lifespan would be longer with a transplantation than without. The evaluation aims at investigating whether the patient is eligible for a

المنارة للاستشارات
ww

liver transplantation and if there are any contraindications to undergo the surgery. Contraindications can be malignancies outside of the liver or large tumours inside of the liver, substance abuse, active infections, medical non-compliance, severe malnutrition/sarcopenia, or other diseases and condition affecting the ability to survive surgery, such as severe heart failure or respiratory illnesses. Different centres around the world have slightly different routines for which factors are evaluated. At Karolinska University hospital it is mandatory to have a nutritional assessment by a dietitian during the pre-transplant evaluation. The dietitian's assessment aims at identifying risk factors regarding the nutritional status as well as performing nutritional interventions in order to optimise the nutritional status.

A liver transplant evaluation normally takes around two weeks, and after undergoing all mandatory procedures the results are evaluated at a multi-disciplinary conference. The conference concludes whether or not the patient will be accepted and placed on the waiting list for a liver transplantation. Sometimes the result from the conference is that the patient needs additionally procedures for further investigation.

A challenge in liver transplantation is that it is mainly performed with grafts from deceased donors which means that the length of the waiting time is unpredictable. A patient under consideration for liver transplantation needs to receive care to eliminate the risk of developing contraindications for surgery during the waiting time, including optimising nutritional status to decrease the risk of complications during the waiting time and after liver transplantation (79). The recommendations involve, among others, to be physical active and maintain or improve current nutritional status and the dietitian is therefore an essential member of the healthcare team that cares for patients both before and after a liver transplantation. The waiting time is an uncertain time for the patient, and it is unpredictable how long each patient will wait. The length of the waiting time depends on the patient's blood group, how many other patients are waiting at the same time and how sick each patient is as well as organ accessibility. Patients can be prioritised according to the principle "sickest first", which means that the patient who is sickest will receive a liver transplantation first rather than the patient who has waited the longest. The waiting time can range from 1 day up to more than a year. The waiting time is usually 3-9 months at Karolinska University Hospital.

Survival after liver transplantation has improved significantly to > 90% at one-year (80). The high survival rate is attributed to significant advances in immunosuppression therapy, surgical techniques and early detection of post-operative complications. After liver transplantation different complications can arise such as bile leakage, bleeding, rejection and infections. Infections is one of the most common causes for mortality within 6 months after liver transplantation while death from tumour recurrence or tumour *de novo* is more common late after liver transplantation (78).

المنارة للاستشارات

ww

More than 7000 liver transplantations are performed annually in Europe (78). In Sweden, the first liver transplantation was performed in 1984 at the Huddinge Hospital. As of today, liver transplantation is performed in two centres in Sweden: Sahlgrenska University Hospital in Gothenburg and Karolinska University Hospital in Stockholm together perform 150-200 liver transplants annually (81). In the Nordic countries, the overall survival rate was 91% at 1 year and 71% at 10 years for patients transplanted between 2004-2013 (82). The one-year survival rate was 91.7% for patients transplanted between 2009-2017 at Karolinska University Hospital (unpublished data).

2.5 Causes of malnutrition and sarcopenia in liver cirrhosis

Malnutrition in liver cirrhosis is caused both by an impaired food intake, malabsorption and altered macronutrient metabolism (83). Changes in the liver metabolism together with reduced food intake, nutrient malabsorption and altered energy consumption (84) can negatively affect the nutritional status. A reduced food intake in patients with liver cirrhosis can be caused by different disease related symptoms. Common problems include loss of appetite, early satiety, nausea and functional dyspepsia. These symptoms can be assessed and quantified as NIS. Restrictive diets, for example salt-reduced diets, may cause a low energy intake. The cognitive dysfunction in hepatic encephalopathy can involve difficulties to remember to eat or a reduced food intake. Iatrogenic fasting during hospitalisation can further reduce energy intake. Ascites, delayed gastric emptying and impaired gut motility can cause nausea and early satiety (85). Loss of appetite is frequently described by many patients and can be caused by other NIS or by an up-regulation of TNF-α and leptin (86). Altered taste can be caused by zinc deficiency (87) or by mouth dryness because of use of diuretic medicine. In patients with active substance abuse such as alcoholism there is a risk for poor and irregular dietary intake (88).

Malabsorption can occur in cirrhotic patients due to multiple factors such as portosystemic shunting, intraluminal bile acid deficiency as a result of decreased bile production, chronic pancreatitis secondary to alcohol abuse or small intestinal bacterial overgrowth (89). In patients with portosystemic shunting, blood from the abdominal organs which should be drained by the portal vein into the liver is instead shunted to the systemic circulation. A part of the toxins, proteins and nutrients absorbed by the intestines bypass the liver and are shunted directly into the systemic circulation.

Alterations in glucose metabolism such as reduced glycogen storage, hyperinsulinemia, decreased glucose oxidation, glucose intolerance and diabetes mellitus can affect nutritional status and can potentially be treated with nutritional interventions.

المنارة للاستشارات
ww

Patients with liver cirrhosis display increased gluconeogenesis, fat oxidation and protein catabolism after overnight fasting. Increased protein catabolism may develop even in early stages of liver cirrhosis and increases as the liver function deteriorates. Increased protein synthesis and concomitant increased protein degradation may explain the increased protein requirements in liver cirrhosis (84, 90, 91).

2.6 The impact of nutritional status in chronic liver disease

Malnutrition, sarcopenia, obesity and sarcopenic obesity may worsen the prognosis of patients with liver cirrhosis and increase mortality (21, 92, 93). The first score that was developed in 1964 to classify surgical risk in patients with cirrhosis, by C.G. Child, included nutritional status as one variable in the score (94). Nutritional status was difficult to objectively evaluate and was deemed too subjective to include in the score and was therefore removed in the later versions of the Child-Pugh score (76). The MELD score does not take nutritional status into account (95), but there has been some effort recently to include muscle mass, and two different scores have been developed: Muscle-MELD score (96) and MELD-Sarcopenia (97). The MELD-sarcopenia score provides improved mortality estimation in cirrhosis by adding adds 10 points to the MELD score if a patient is suffering from sarcopenia. This demonstrates the prognostic importance of sarcopenia. The performance of MELD-sarcopenia is better in patients with low MELD scores. The predictive values of these scores are yet to be validated in larger cohorts before they can be applied clinically, such as for liver transplantation organ allocation.

The prevalence of malnutrition differs between various countries, severity of liver disease and depends on which method is used for identifying malnutrition. The nutritional status and the severity of liver cirrhosis are closely linked. The risk of malnutrition increases as the liver disease progresses. One of the first studies using anthropometry to assess malnutrition in patients with liver disease showed that the prevalence increased from 20% in Child-Pugh A to over 60% in Child-Pugh C (30). The prevalence of malnutrition in patients with chronic liver disease depends which method is used for nutritional assessment (30, 98, 99). Ferreira et al. (100) used different methods to assess the nutritional status of 159 patients on the waiting list for liver transplantation and highlight the disparities in prevalence of malnutrition depending on the method used: BMI 6.3 %, TSF 25.8%, MAMC 38.4%, SGA 74.7% and HGS 80.8%. In a study of 300 patients with advanced liver disease, more than 75% of the patients were malnourished and almost 40% were moderately to severely malnourished (99).

Recent studies have focused on assessment of muscularity at the third lumbar vertebrae (L3) transverse plane measured with CT. A retrospective review of CT images

المنارة للاستشارات

ww

of 142 patients (98) under evaluation for liver transplantation identified sarcopenia in 41% and found sarcopenia to be an independent predictor of mortality on the waiting list after adjustment for age and MELD score. The prevalence increased from 10% in Child-Pugh A to 34% in Child-Pugh B and 54% in Child-Pugh C. In a study of 234 patients with end-stage liver disease (101), more than 50% of those with BMI in the obese range were cachectic on CT body composition analysis.

In a study of 366 living-donor liver transplanted patients, sarcopenia was defined as reduced skeletal muscle mass measured with CT and low muscle strength measured with hand grip strength. Patients with sarcopenia had greater incidence of postoperative complications of Clavien-Dindo grade IV and longer postoperative hospital stay (102). Sarcopenia was also a significant predictor of 6-month mortality. Severe muscle depletion is associated with an increased length of stay after liver transplantation (103). Sarcopenia has been shown to impair the prognosis in liver cirrhosis (23). For patients undergoing liver transplantation, malnutrition has been reported to affect length of stay (LOS), rate of serious infections and mortality (7, 98). Malnutrition is associated with mortality but also the risk of developing HE and ascites (104, 105). In one of the few randomised trials to assess nutritional therapy in patients with minimal hepatic encephalopathy, Maharshi et al found that patients achieving the recommended energy- and protein intake were less likely to develop overt HE (106).

The prevalence of sarcopenia depends on country, age, gender distribution and severity of liver disease of the study population. Studies involving participants with a higher proportion of patients with more severe liver disease tend to report a higher frequency of sarcopenia. Table 2 highlights these disparities in prevalence of sarcopenia and muscle mass depletion in different studies.

المنارة للاستشارات
ww

Table 2. Prevalence of sarcopenia or muscle mass depletion in different studies investigating skeletal muscle mass index with computed tomography

Reference	Country	N	Year	Male	Age	MELD	Child-Pugh B/C	Sarcopenia/ muscle mass depletion
Meza-Junco et al (107)	Canada	116	*	85%	58	9	47%	30%
Wang et al (108)	USA	292	2011-2014	66%	61	15	73%	38%
Montano-Loza et al (21)	Canada	678	2000-2013	67%	56-58	13-16	79-91%	43%
Wells et al (109)	New Zealand	107	2004-2010	71%	54	12	66%	43-53%
Hanai et al (23)	Japan	130	2004-2012	58%	66	11	74%	68%
DiMartini (110)	USA	338	2005-2008	66%	55	20	*	68%
Giusto et al (35)	Italy	59	2011-2013	78%	59	13.1-13.5	66%	76%

*Information not available in the published article. The column "Year" refers to time period when the data collection was performed, not the year when the study was published.

Obesity has adverse effects on health in many situations, also in chronic liver disease where obesity can affect progression of the disease. Obesity is considered one of the major risks for developing non-alcoholic fatty liver disease (NAFLD), and NAFLD represents the hepatic part of the metabolic syndrome (111). Obesity is also considered an independent risk factor for fibrosis progression (112). In patients with Hepatitis C, the risk of progression to liver cirrhosis or decompensation has been shown to increase by 14% for each increase in BMI quartile (113). An intervention study with diet and exercise to lose weight in obese patients with compensated cirrhosis, showed that portal pressure and body weight was reduced after a 16 week long program (114). The results from this study suggest that obesity promotes portal hypertension. In context with the growing understanding of the role of obesity in liver disease it is important to acknowledge that obesity does not rule out malnutrition or sarcopenia. Sarcopenic obesity is prevalent in patients before and after liver transplantation (21, 115, 116) and patients with sarcopenic obesity have worse survival rate than patients with sarcopenia alone (21). Patients with sarcopenic obesity have a risk of adverse outcomes both from obesity and from low muscle mass, the risk can be higher than the risk induced by each of the two conditions alone.

المنارة للاستشارات

ww

2.7 Quality of life in chronic liver disease

Quality of life is a concept that encompasses both positive and negative aspects of life. Health-related quality of life (HRQOL) "*is a subjective measure depending on an individual's perception of the impact of disease and/or treatment on their health status"* (117). Patients with chronic liver disease have been reported to have an impaired HRQOL (118, 119). Low HRQOL has been shown to be correlated with grade of liver disease (120, 121). Complications of liver disease such as ascites and hepatic encephalopathy have a negative impact on quality of life (122-124). Ascites and hepatic encephalopathy may also increase the risk of developing eating difficulties. These complications can to some extent be treated with nutritional interventions (125, 126) and HRQOL can potentially improve if symptoms are treated. HRQOL can be studied with questionnaires such as the Medical Outcomes Study Short Form-36 or with disease-specific questionnaires such as the Chronic Liver Disease Questionnaire (CLDQ) (127).

A study of 1175 patients with chronic liver disease in the Netherlands found HRQOL in chronic liver patients to be determined by disease severity, joint pain, depression, decreased appetite and fatigue (118). Another study of patients with liver disease found the presence of gastrointestinal symptoms such as reflux, abdominal pain, constipation, indigestion and diarrhea to be correlated with weight loss and poor quality of life (62).

Some studies have found conflicting results. Older age and measures of disease severity were associated with poorer HRQOL and family income was positively correlated with CLDQ (120). CLDQ scores were however not related to age, gender, or level of education in another study (128). Two studies found HRQOL scores to be decreased with worsening of liver function (119, 122) while another study found psychiatric comorbidity and active medical comorbidity, but not severity of the liver disease according to the Child-Pugh score, to determine reduced HRQOL in patients with chronic liver diseases (129). In a Danish prospective study of 92 patients with chronic liver disease, Child-Pugh score, non-alcoholic etiology of cirrhosis, and BMI were predictors of poor HRQOL. The BMI predicted poor HRQOL independently of the presence of ascites (130).

Some authors have studied the impact of malnutrition on HRQOL. In an Indian study by Panagaria et al, the severity of liver disease was negatively correlated with quality of life and energy intake was positively correlated with quality of life (131). In a recent study of 127 patients with liver cirrhosis, 59.8% reported a reduced HRQOL and a strong association with malnutrition was found (132).

The impact of nutritional status on quality of life has also been reported in other groups of patients. In a systematic review, 24 out of 26 articles showed that a good nutrition status is also associated with a higher quality of life in patients with cancer (133).

المنارة للاستشارات
ww

3 AIMS

The overall aim of this thesis was to increase the knowledge of nutritional assessment in chronic liver disease before and after liver transplantation. The specific aims of this thesis were:

- To study the prevalence of malnutrition among patients listed for liver transplantation and to investigate associations between body composition parameters measured with DXA and outcome after liver transplantation. (*Study I*)
- To perform inter-method comparisons between three measures of muscle mass in patients eligible for liver transplantation: fat free mass index (FFMI) measured by DXA, appendicular skeletal muscle mass (ASMI) measured by DXA and skeletal muscle mass index (SMI) measured by CT. (*Study II*)
- To assess the prevalence and severity of NIS in patients with chronic liver disease under evaluation for liver transplantation and to explore associations between NIS, malnutrition and HRQOL. (*Study III*)
- To compare measured REE with predicted REE calculated by HB and with energy requirements determined by the fixed factors (25, 30 and 35 kcal/kg/day), to identify clinical factors associated with REE early after liver transplantation, and to explore whether data from our cohort could enable constructing an equation that predicts energy requirement better than the HB. (*Study IV*)

المنارة للاستشارات

ww

4 MATERIAL AND METHODS

4.1 A summary of the studies

An overview of the study design of each study included in the thesis is describe in Table 3.

Table 3. An overview of the studies included in the thesis

Study	I	II	III	IV
Design	Retrospective Cohort	Retrospective Cohort	Cross-sectional	Retrospective Cohort
Study population	Liver transplanted	Liver transplanted	Undergoing liver transplantation evaluation	Liver transplanted
Data source (s)	DXA, Medical records, local transplant registry	DXA, CT, Medical records, local transplant registry	Questionnaires, DXA, Anthropometry, Medical records	IC, Medical records, local transplant registry
Study period	2009-2012	2009-2012	2016-2018	2011-2018
Inclusion criteria	Chronic liver disease, ≥ 19 years of age, DXA performed at Karolinska	Chronic liver disease, ≥ 19 years of age, had a DXA and CT scan within 30-d	Chronic liver disease, ≥ 18 years of age	LT with a graft from deceased donor, ≥ 18 years of age, IC done in within 30-d postop
Exclusion criteria	Previous LT, multiorgan transplantation	Previous LT, multiorgan or hyper urgent transplantation, non-cirrhotic patients.	Age <18 years, inability to fill in the questionnaires	Multiorgan or hyper urgent transplantation
Main factors analysed	Prevalence of muscle mass depletion and association with outcomes post-LT	Comparison of DXA and CT in measuring muscle mass depletion	Frequency of nutrition impact symptoms and association with malnutrition and HRQOL	mREE compared with HB and fixed factors, associations with pre- and postoperative factors
Statistical analysis	Chi-square or Fisher test, Mann-Whitney, logistic and multiple linear regression.	Chi-square or Fisher test, One-way analysis of variance or Mann-Whitney, Pearson correlation coefficient.	Chi-square, t-test, median regression, multinomial logistic regression.	Lin's concordance correlation coefficient, Bland-Altman plots, Chi-square, Kruskal- Wallis test, multiple linear regression, stepwise regression

DXA; dual-energy x-ray absorptiometry, LT; liver transplantation, CT; computed tomography, HB; Harris & Benedict equation, HRQOL; health-related quality of life, IC; indirect calorimetry, mREE; measured resting energy expenditure, REE; resting energy expenditure, TEE; total energy expenditure

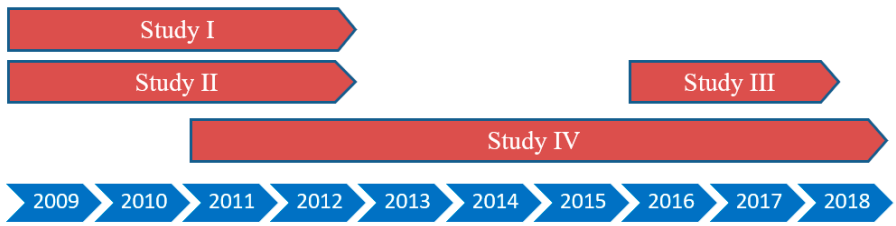
المنارة للاستشارات

ww

4.1.1 Inclusion and exclusion

This thesis includes studies on patients undergoing liver transplantation evaluation *Study I, II, III*) and liver transplantation (*Study I, IV*) at Karolinska University Hospital in Stockholm, Sweden. The four studies in this thesis are based on different study cohorts generated by different methods, and the populations are partly overlapping (Figure 4).

Figure 4. Overview of study periods



Data on consecutive liver transplantations between 2009 and 2012 were retrospectively reviewed for *Study I and II*. In total 228 liver transplantations were performed on adult patients during this time period. Patients with non-chronic liver disease, previous liver transplantation or multi-organ transplantation were excluded as well as patients who did not have a DXA scan or a formal nutrition assessment performed at Karolinska University hospital. In total 109 patients fulfilled the inclusion criteria: age above 18, chronic liver disease and had a DXA-scan performed and consisted the cohort for *Study I*. Patients from the same cohort which had both a DXA and a CT scan performed within 30-days during the pre-transplant evaluation was included in *Study II*.

Adult patients with chronic liver disease under evaluation for liver transplantation during the time period February 2016 until February 2018 were invited to participate in *Study III*. In total 133 patients accepted participation and signed the study informed consent form. Exclusion criteria were age < 18 years, inability to fill in the questionnaires for example because of language difficulties or severe hepatic encephalopathy.

Study IV was a retrospective analysis of patients who underwent liver transplantation between 2011-2018. Inclusion criteria were age ≥ 18 years at time of liver transplantation, liver transplantation with a graft from a deceased donor and had an indirect calorimetry performed within 30 days after a liver transplantation. Exclusion criteria was multi-organ transplantation or transplantation because of acute liver failure.

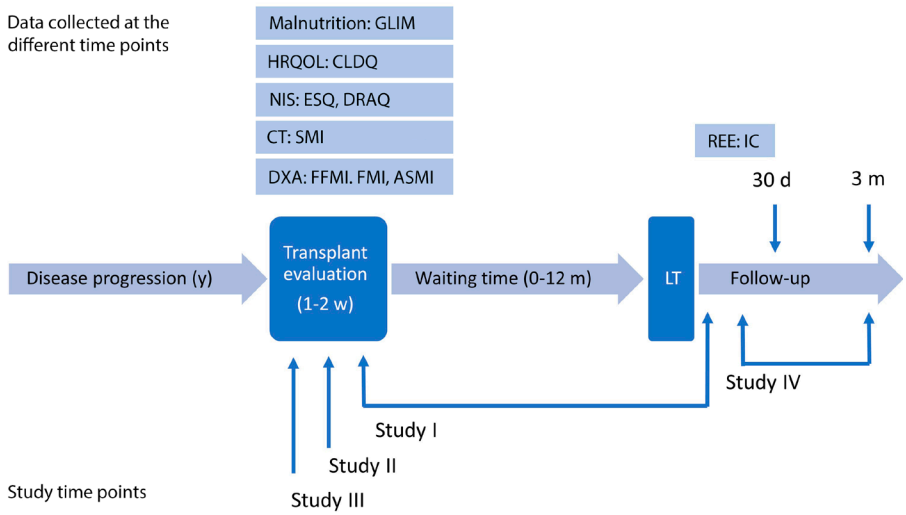
المنارة للاستشارات

ww

4.2 Data sources

Figure 5 presents an overview of when different data was collected in the four studies included in this thesis.

Figure 5. Overview of the four studies and data collection time points



ASMI; appendicular skeletal muscle mass index, CLDQ; chronic liver disease questionnaire, CT; computed tomography, DXA; dual-energy x-ray absorptiometry, DRAQ; disease related appetite questionnaire, ESQ; eating symptom questionnaire, FFMI; fat-free mass index, FMI: fat-mass index, GLIM; The Global Leadership Initiative on Malnutrition, HRQOL; health-related quality of life, IC; indirect calorimetry, LT; liver transplantation, REE; resting energy expenditure, SMI; skeletal muscle mass index

4.2.1 Medical characteristics and post-transplant outcome

In all four studies information was collected from medical charts and the local liver transplant registry Ekvator. Information was double-checked in the chart and in the registry to minimise the risk of error and missing data. The Child-Pugh and MELD scores were collected to grade severity of liver disease. Allocation of organ at Karolinska University Hospital is based on Child-Pugh score in combination with comorbidity and performance status and not primarily MELD based. No extra MELD points are given for e.g. hepatocellular carcinoma (HCC). Infections and LOS after liver transplantation was studied in *Study I*. Severe infections were defined as systemic or requiring intravenous or prolonged courses of antimicrobials within 30 days of liver transplantation. LOS at the transplant center as well as the ICU was collected. Surgical complications from liver transplantation up until 3 months postoperatively were classified according to the Clavien-Dindo classification (134) in *Study IV*. Clavien-Dindo grade complications from none to V.

المنارة للاستشارات
ww

Grade III-IV are considered more severe complications where grade III requires surgical, endoscopic or radiological intervention, grade IV is life-threatening complication and grade V is death of patient.

4.2.2 Body composition

A DXA-scan to screen for osteoporosis is performed during the pre-transplant evaluation for all patients referred to Karolinska University Hospital. In some regions of Sweden, DXA is performed at the referring hospital, and those patients were not included in *Study I-III*. The DXA scans performed at Karolinska University hospital were performed with a fan-beam DXA (GE Lunar iDXA; system number ME +200030; GE Lunar Corp., Madison, WI, USA). The reported precision for the DXA machine used in Study *I-III* is high with coefficient of variations of 0.5% for lean tissue mass and 0.82% for total fat mass (135).

Data on fat mass, lean soft tissue and bone minerals were collected from the DXA scans for *Study I-II*. Fat mass was adjusted for height to calculate fat mass index (FMI). Lean soft tissue together with bone minerals constitute fat free mass which was also adjusted for height to calculate FFMI. For S*tudy II-III* ASMI was calculated from appendicular lean soft tissue mass (kg) divided by squared body height.

CT-scans performed during the pre-transplant evaluation were used to measure body composition in *Study II.* Each pixel from the scans attenuation is reported in Hounsfield units (HU). HU thresholds used in the study was -150 to -30 for fat (136) and -29 to +150 for muscle (137). The overlapping area -29 to + 30 was quantified separately together with average attenuation to quantify fat infiltration in the muscle (138). The tube voltage for CT was 100 to 120 kV. A transverse single 5-mm-thick image from the middle of the L3 vertebra was extracted from each scan. The software Image J 1.50c from the National Institutes of Health, USA, (139) was used for segmentation. The psoas and paraspinal muscles (erector spinae, quadratus lumborum), and the abdominal wall muscles (transversus abdominis, external and internal obliques, rectus abdominus) were segmented as well as visceral and subcutaneous adipose tissues at the L3 level.

4.2.3 Resting energy expenditure

REE was extracted from indirect calorimetry measurement performed for clinical reasons. REE was measured by indirect calorimetry, using Fitmate® (COSMED, Rome, Italy), previously validated for REE measurements in adults (140, 141). The patients were rested in a supine position for more than 30 minutes and were asked to remain motionless and awake during the test. Measurements were performed after overnight fast (>8 hours of fasting), or 4 hours of fasting. The device was automatically calibrated before each measurement. The volume of inspired oxygen

المنارة للاستشارات

ww

was collected using a face mask with integrated bacterial filter. The exhaled gas was collected over 20 minutes, and the gas collected over the first five minutes was discarded. The mean volume of inspired oxygen per minute was used to calculate the REE according to the Weir (142) formula. Hypermetabolism was defined as a measured REE (mREE) ≥120% of the predicted value from HB; normometabolism, as a mREE within 80-119% of the predicted value, and hypometabolism, as a mREE < 80% of the predicted value (143). Total energy expenditure (TEE) was calculated as mREE x physical activity level 1.2 (144-146) to enable comparisons with the fixed factors.

4.2.4 Questionnaires

The chronic liver disease questionnaire (CLDQ) was developed in USA twenty years ago (147), and has been extensively used in liver research. In *study III*, a validated Swedish version was used (148). The CLDQ includes 29 questions graded on a seven-point scale from 1 (all the time) to 7 (none of the time). The questions comprise six domains; abdominal symptoms, fatigue, systemic symptoms, activity, emotional functioning and worry. The questionnaire gives domain scores as well as a total CLDQ score.

Two different questionnaires were used to assess the presence of NIS: The Eating Symptom Questionnaire (ESQ) and the Disease-Related Appetite Questionnaire (DRAQ). The ESQ and DRAQ were developed by means of dietitian led focus groups and patient interviews with the purpose to investigate NIS in patients at risk of developing malnutrition or patients suffering from malnutrition (70). The questionnaires have previously been used to investigate NIS in patients with different cancers (149) and gastrointestinal diseases (68). No validation study has been done since there is no gold standard for investigating NIS. The ESQ encompasses a list of symptoms that could affect eating and/or appetite and whether any of these symptoms was experienced during the last two weeks on a five-level Likert scale, from no trouble at all to severe symptoms. The ESQ includes an open question at the end of the questionnaire where the respondent can describe any additional symptoms not included in the list. The DRAQ has a different design and consists of 11 questions relating to appetite, hunger and other symptoms that may affect eating.

A general population of Swedes between 18-74 years of age were also asked to fill in ESQ and DRAQ to see if the prevalence of NIS were different between the cohort of patients with chronic liver disease and the general population. Two of the questions from DRAQ were removed for the general population ("Compared with when I was healthy food tastes…" and "How long has the disease affected your appetite?"). Consumer Intelligence, a company that provides target groups for

المنارة للاستشارات
ww

use in connection with internet-based research sent out questionnaires to approximately 3950 men and women between the ages of 18-80 which resulted in complete questionnaires from 506 individuals nationally representative according to gender, age and geographical region. This data was not included in the published paper regarding nutrition impact symptoms (*Study III*), although some results are presented in the result section of this thesis.

4.3 Defining malnutrition and muscle mass depletion

Different methods to define malnutrition were used in *study I* and *study III*. In *study I*, cut-offs for FMI and FFMI were <5th percentile according to age and gender from a reference population (150) were used to diagnose malnutrition as well as assessment performed by a dietitian. A retrospective review was performed of the nutritional assessments performed by dietitians during the pre-transplant evaluation. Between 2009-2012 the dietitians as Karolinska University Hospital went through a process of structuring their assessment according to the Nutrition Care Process (1). The definition of malnutrition changed slightly during the study period and in some cases it was not clear during which time period the patient had lost weight. For that reason, malnutrition was defined as weight loss > 10% (unspecified time period) in combination with eating difficulties or BMI <20. In *study II* muscle mass depletion was defined according to the following cut-offs: age and sex adjusted FFMI indices <10th percentile (150), ASMI 7.59 kg/m^2 for men and 5.47 kg/m^2 for women (151). SMI cut-offs for muscle depletion were <43 cm^2/m^2 for men with BMI <25 kg/m^2 and <53 cm^2/m^2 for BMI >25 kg/m^2 and <41 cm^2/m^2 for women in all BMI ranges (52). SGA was used to diagnose malnutrition during the time period 2016-2018 (6) and was presented for descriptive purposes in *Study III*. The GLIM criteria published in 2018 (15) were retrospectively assessed to diagnose malnutrition in *Study III* and used for all the statistical analysis. The cut-offs used for reduced muscle mass according to ASMI in *Study III* were: 7 kg/m^2 for men and 6 kg/m^2 for women (152).

المنارة للاستشارات

4.4 Statistical analysis

The statistical test that were used in *Study I-IV* are summarised in Table 3. Descriptive statistics were used for categorical (number and percentage) and continuous variables (mean and standard deviation or median and inter-quartile range (IQR) according to distribution). A p-value <0.05 was considered statistically significant.

4.4.1 Study I

Univariate analysis was done with Chi-square or Fisher's exact test for categorical data, and Mann–Whitney for continuous variables with skewed distribution. A logistic regression model was fitted for the dichotomous outcome variable of post-operative infections up to one month after liver transplantation. The model adjusted for age, sex, body composition (measured as FMI or FFMI), indication for liver transplantation, causes of end-stage liver disease, weight loss, nutritional assessment by dietitian, time on the waiting list, MELD score at the time of liver transplantation, perioperative bleeding, need for dialysis, duration of mechanical ventilation, and length of stay in the ICU and hospital. Model fitness was assessed with the Hosmer-Lemeshow test.

Multiple linear regression analyses, with the length of stay in the ICU in the first model and duration of hospitalisation in the second as outcome variables, were constructed separately. The models adjusted for age, sex, body composition (measured as FMI or FFMI), indication for transplantation, causes of end-stage liver disease, weight loss, nutritional assessment by dietitian, time on the waiting list, MELD score at the time of liver transplantation, post-operative bleeding, need for dialysis, and duration of mechanical ventilation. In the model with the duration of hospitalisation, adjustments for the length of stay in the ICU and post-operative infections up to 1 month were also included. In selecting variables for the multivariate analysis, we used a combination of predefined predictors based on literature search, and any significant variable in the univariate analyses. Thus, we did not only include significant predictors from the univariate analyses in the final multivariate model, as such an approach might wrongly reject potentially important variables (153). Testing for influential cases and outliers in regression models was also done, and such cases were excluded from the primary analysis. A further sensitivity analysis was then done with the inclusion of these outliers to check for changes in the significance level of predictors. Statistical analyses were performed with the SAS® software version 9.4 (Cary, NC).

المنارة للاستشارات

4.4.2 Study II

Intra-class correlation (ICC) scores between two independent raters were calculated for 20 of the patients. Data were tested for normal distribution with the Shapiro-Wilks test. For categorical variables, the Chi-square test or the Fisher test was used for group comparisons. To detect any differences between patients with and without muscle mass depletion, one-way analysis of variance was used for variables of symmetric distribution and the Mann-Whitney test for variables of asymmetric distribution. Correlations between continuous variables were assessed using Pearson correlation coefficients. The software used for the analysis were SPSS version 19 (IBM, Armonk, NY, USA) and SAS (SAS Institute, Cary, NC, USA) for Windows.

4.4.3 Study III

To test for differences in distributions, Chi-square test was used for categorical data and t-test for continuous variables. Median regression was used to assess the association between CLDQ and malnutrition. Multinomial logistic regression was used to analyse which NIS were predictors of malnutrition according to GLIM, after adjusting for sex, Child-Pugh class and ascites. The statistical analyses were performed with SPSS version 25 (IBM, New York, NY, USA) and Stata version 15 (StataCorp, College Station, TX, USA).

4.4.4 Study IV

Agreement between mREE and predicted REE and fixed factors were assessed with Lin's concordance correlation coefficient (CCC) that combines measures of precision and accuracy, Bland-Altman plots, and 95% confidence intervals (CI). Differences in distribution between groups of hypo-, normo- and hypermetabolism were tested with Kruskal-Wallis test for continuous variables and Chi-square test for categorical data.

A multiple linear regression with robust standard errors was performed using the mREE as a dependent variable to test for associations between variables and mREE. Robust standard errors were used to avoid homoscedasticity.

A new predictive equation was constructed for REE using predictive coefficients devised from using stepwise regression analysis of variables that were significantly associated with mREE in the multiple linear regression. The agreement of this new devised formula for predicting REE with mREE was tested with CCC. The statistical analyses were performed with SPSS version 25 (IBM, New York, NY, USA) and Stata version 15 (StataCorp, College Station, TX, USA).

المنارة للاستشارات

ww

5 ETHICAL CONSIDERATIONS

All studies were conducted in accordance with the Declaration of Helsinki. The studies within this thesis were approved by the Regional Ethical Review board in Stockholm, Sweden (*Study I and II:* 2012/2018-31/1, *Study III:* 2015/2045-31/2 and *Study IV:* 2017/830-31/1, 2019-03646). Informed written consent was signed by all participants in S*tudy III*.

The Declaration of Helsinki was developed to protect human subjects rights and health. The four principals of medical ethics (to do good, respect for autonomy, do no harm, be just) have been considered in this thesis (154). Research should be conducted for the benefit of others. The purpose of this thesis is to do good: to gain knowledge on how to improve nutritional assessment in patients undergoing liver transplantation in order to identify who needs treatment. The results can be beneficial for future patients undergoing liver transplantation. The second principle, respect for autonomy, is taken into consideration during anonymisation of the data. All data was coded, and all analyses were performed on a group level, thus minimising the risk of any individual being identified. In *Study III*, informed consent was collected. In *Study III* it is important to acknowledge that a pre transplant evaluation is an exposed position for a patient, where the patient is evaluated if they will be allowed to receive a liver transplantation. Information about the study was sent to the patient before the visit to the dietitian. When the nutritional assessment was finished the patient was asked about study participation. It was emphasised that participation was voluntary and could be stopped at any point without explanation. The study was constructed in a way to not cause any harm except for the time spent on filling out the questionnaires. There was no direct benefit for those who participated. The potential privacy violation that can arise from answering questions about symptoms and quality of life was handled by the patient having the right to refuse or abort participation in the study at any time and by anonymisation of data during analysis. All patients under evaluation for liver transplantation during the study period were asked for participation. The study however excluded patients who did not understand Swedish or suffered from severe encephalopathy. The ability to independently make decisions about participation is reduced when an interpreter needs to be used to translate information or when the level of consciousness is reduced. The principle of justice could be influenced since all persons should be treated equally and some patients were not asked to participate because of the above reasons.

The studies in this thesis are not experimental and therefore fulfil the principle of not harming the participants.

المنارة للاستشارات

6 RESULTS

6.1 Study participants

A selection of patient characteristics in the different studies are shown in Table 4.

Table 4. Overview of clinical characteristics in *Study I-IV*

Study	I	II	III	IV
Number of patients	106	53	133	143
Male, number (%)	68 (64)	37 (70)	97 (73)	106 (74)
Age, median (IQR)	55 (16)	57 (16)	59 (19)	51 (19)
MELD, median (IQR)	13 (7)	11 (8)	12 (7)	12 (9) *
Child-Pugh score, n (%)				n/a
A	32 (30)	27 (51)	46 (35)	
B	41 (39)	14 (26)	64 (48)	
C	33 (31)	12 (23)	23 (17)	
Ascites, n (%)	44 (42)	19 (36)	50 (38)	47 (36)**
Hepatocellular carcinoma, n (%)	36 (34)	28 (53)	51 (38)	39 (27)
Cause of liver disease, n (%)				
Autoimmune	33 (31)	16 (30)	49 (37)	57 (40)
Viral with/without alcohol	50 (47)	27 (51)	30 (23)	34 (24)
Alcohol	10 (9)	4 (8)	28 (21)	21 (15)
NASH***	x	x	14 (11)	x
Other	13 (12)	6 (11)	12 (9)	31 (22)

IQR; interquartile range, MELD; model for end stage liver disease, NASH; non-alcoholic steatohepatitis *MELD at day before liver transplantation, **14 missing data, *** Patients with NASH were included in the group “other” in Study I, II and IV. Information on ascites and hepatocellular carcinoma was collected on the day before liver transplantation for Study IV, for Study I-III the data refers to the present of this condition during the pre-transplant evaluation.

6.2 Nutritional status

Several techniques to study malnutrition and body composition were used in this thesis. The prevalence of malnutrition was 2-20% in *Study I* and 32% in *Study III*. Muscle mass depletion varied between 30-40% in *Study II*. Table 5 describes the different cut-offs that were used for muscle mass depletion in the different studies.

المنارة للاستشارات

ww

Table 5. Prevalence of muscle mass depletion and cut-offs used in Study I-III

	Study I		Study II		Study III	
	Cut-off	Below cut-off	Cut-off	Below cut-off	Cut-off	Below cut-off
FMI	Age and sex adjusted < 5th percentile	All 9% M 6% F 16%				
FFMI	Age and sex adjusted < 5th percentile	All 15% M 20% F 5%	Age and sex adjusted < 10th percentile	All 30% M 38% F 13%		
ASMI			M <7.59 kg/m^2 F <5.47 kg/m^2	All 39% M 40% F 38%	M <7 kg/m^2 F <6 kg/m^2	All 23% M 20% F 30%
SMI			M <43 cm^2/m^2 for BMI <25 kg/m^2 and <53 cm^2/m^2 for BMI >25 kg/m^2 F <41 cm^2/m^2 in all BMI ranges	All 40% M 27% F 69%		

FMI; fat mass index, FFMI; fat-free mass index, ASMI; appendicular skeletal muscle mass index, SMI; skeletal muscle mass index, M; male, F; female.

Study I and II: Coin et al. Fat-free mass and fat mass reference values by dual-energy X-ray absorptiometry (DEXA) in a 20-80 year-old Italian population (150)

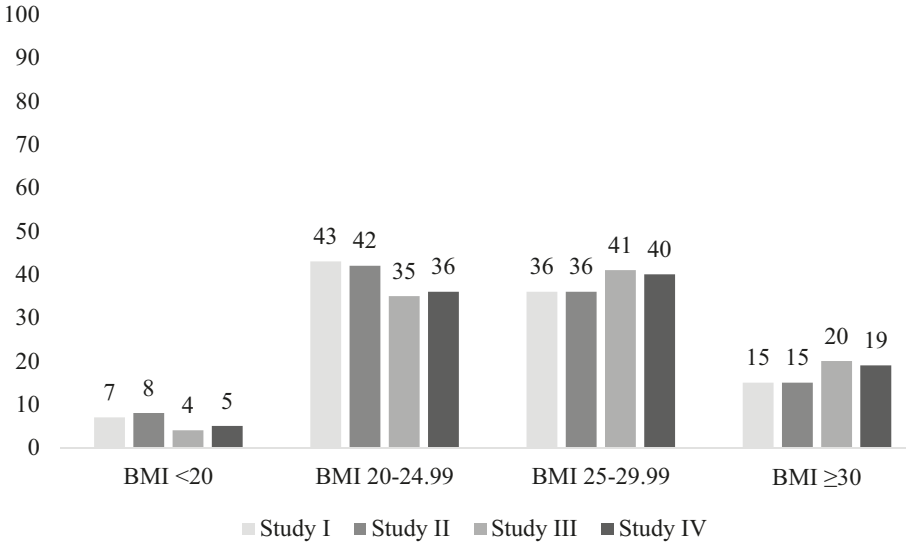
Study II: Martin et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index (52)

Study III: Cruz-Jentoft et al. Sarcopenia: revised European consensus on definition and diagnosis (17)

The median BMI was 25.1 kg/m² in *Study I* and *II*. In *Study III* and *IV*, the median BMI was 26 kg/m². The majority of patients in all four studies had a BMI in the range between normal weight and overweight and 15-20% were obese (Figure 6).

المنارة للاستشارات

Figure 6. Percentage of patients classified within different BMI-groups across the studies



BMI; body mass index. BMI at time of pre-transplant evaluation for Study I, II, III. BMI at pre-transplant day 0 for Study IV.

Weight loss during the last six months was found in 45% of the patients in *Study I*, with 17% reporting ≥ 5% weight loss and 20% had lost ≥ 10% of their weight. In *Study III*, 47% of the participants reported some degree of weight loss, where 14% had lost ≥ 5% and 6% had lost ≥ 10% of their body weight.

6.3 Study I

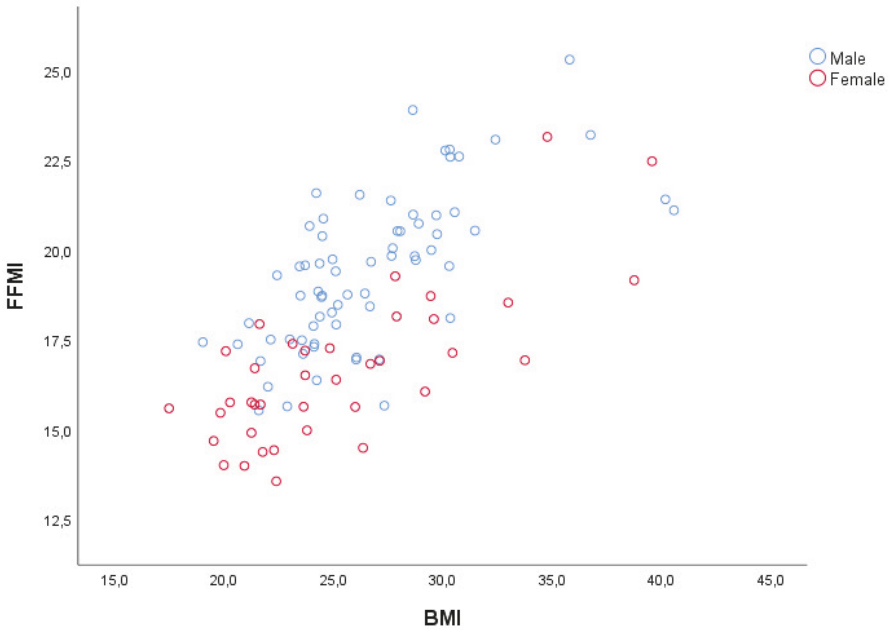
Hundred and nine patients who underwent liver transplantation during the study period 2009-2012 had a DXA-measurement performed during the pre-transplant evaluation and were included in the study. Three DXA scans were excluded because of ambiguous results and the study cohort therefore consisted of 106 patients. The prevalence of malnutrition depended on assessment method. Body composition measured by DXA during the pre-transplant evaluation was found to provide valuable information, FFMI was associated early post-transplant infections. There were 64% men, and median age was 55 years. The most common aetiologies for end-stage liver disease were viral hepatitis (35%), autoimmune diseases (31%) and alcoholic liver disease (22%). At the day before the transplant, the median Child-Pugh score was 9 (IQR 4) and 42% had ascites.

المنارة للاستشارات

ww

There were large gender differences in body composition. In total 15% of the population had low FFMI according to the age and gender adjusted cut-offs that were used. Low FFMI was present in 20% of the men, and in 5% of the women. The opposite distribution was found for FMI, with 9% of the entire population presenting with low values. Six percent of the men had low FMI and 16% of the women. If the cut-offs previously suggested by ESPEN (155) were to be applied for FFMI, the prevalence would instead be 16 % with a low FFMI, with 8 (21%) women and 9 (13%) men. Figure 7 illustrates the relationship between FFMI and BMI according to gender (not included in the published paper).

Figure 7. Scatterplot FFMI/BMI



BMI; body mass index, FFMI; fat-free mass index

The nutritional assessment performed by dietitians identified 57% at no risk of malnutrition, 39% at risk of malnutrition and 5% as malnourished. When comparing the nutritional assessment with FFMI and FMI, there were no significant difference in FFMI (p=0.142) between the groups. FMI was significantly different in the patients classified as at risk of malnutrition or malnourished (p=0.007).

Thirty seven percent of the patients included in the study developed severe infections within the first 30 postoperative days. In the multivariate analysis with logistic regression, body composition (FFMI) was significantly associated with

المنارة للاستشارات
ww

post-operative infection when measured with FFMI (odds ratio (OR) = 0.67; 95% confidence interval (CI) = 0.45–0.99), in contrast FMI was not significantly associated (OR = 0.85; 95% CI = 0.70–1.02). Longer length of stay in hospital was associated with a higher risk of infection (OR = 1.2; 95% CI = 1.1–1.3), whereas increasing age was associated with a lower risk of post-operative infection (OR = 0.91; 95% CI = 0.85–0.99).

6.4 Study II

Fifty-three patients who underwent a liver transplantation between 2009-2012 had a CT and DXA measurements within a 30-day period during the pre-transplant evaluation and were included in the study. We found that appendicular skeletal muscle mass index measured by DXA ($ASMI_{DXA}$) and skeletal mass index measured by computed tomography (SMI_{CT}) provided similar results when assessing the presence of muscle mass depletion in patients with chronic liver disease. Fat-free mass index measured with DXA ($FFMI_{DXA}$) can be falsely high in patients with ascites.

There were no significant association between SMI_{CT} and liver function measured by Child-Pugh score ($p = 0.366$), aetiology of liver disease ($p = 0.57$) or with the presence of HCC ($p = 0.70$).

Muscle depletion varied among methods and gender. $FFMI_{DXA}$, $ASMI_{DXA}$, and SMI_{CT} were relatively consistent among men ($FFMI_{DXA}$ 38%, $ASMI_{DXA}$ 40%, and SMI_{CT} 27%). There were large discrepancies for women between methods ($FFMI_{DXA}$ 13%, $ASMI_{DXA}$ 38%, and SMI_{CT} 69%).

During the pre-transplant evaluation, thirty-one (59%) patients had a measurement of hand grip strength by a hand grip dynamometer (not in the published paper). Eight (26%) patients showed a significant reduction in muscle strength (HGS≤10th percentile (156)). Of the patients who had HGS measured, sarcopenia (low muscle strength and low muscle mass) was present in 2 (7%) $FFMI_{DXA}$, 5 (16%) $ASMI_{DXA}$ and 3 (10%) SMI_{CT}. A Pearson correlation test was performed between HGS and muscle mass measurements. $ASMI_{DXA}$ and HGS showed the strongest correlation ($r=0.77$, $p =<0.001$), a strong correlation was also found between HGS and SMI_{CT} ($r=0.68$, $p =<0.001$). HGS did not correlate with $FFMI_{DXA}$ ($r=0.25$, $p =0.180$).

There were no differences in measured visceral or subcutaneous fat in muscle depleted patients according to SMI_{CT} compared to patients with no muscle depletion. $ASMI_{DXA,}$ but none of the other body composition parameters, showed statistically significant difference between the patients with and without muscle depletion (Table 6).

المنارة للاستشارات

ww

Table 6. Body composition characteristics during the pre-transplant evaluation according the presence or absence of muscle depletion measured by SMI_{CT}

	All (n= 53)	**Muscle depletion** (n= 21)	**No muscle depletion** (n=32)	***p***
Body composition				
Weight	75.2 (20.5)	67.2 (21)	78.6 (17)	0.186
Height	173 (17)	171 (18)	172.5 (10)	0.507
BMI, kg/m²	25.1 (5.3)	24.4 (6)	25.4 (6)	0.184
Obese BMI ≥ 30, n (%)	8 (15)	2 (10)	6 (19)	0.426
Fat				
Visceral fat, cm²	125 (69.3)	120 (140)	118 (79)	0.891
Subcutaneous fat, cm²	298.1 (137.1)	307 (202)	311 (152)	0.963
Adipose tissue surface area at L3 (cm²) *	423.1 (193.4)	459 (305)	406 (209)	0.731
Adipose tissue index*	143 (62)	138 (91)	145 (84)	0.494
FMI DXA	7.2 (3,6)	7.7 (6)	6.8 (4)	0.651
Muscles				
ASMI DXA **	7.4 (1.5)	6.5 (2.1)	8.0 (1.4)	**<0.001**
FFMI DXA	18.2 (2.3)	17.1 (3.5)	18.4 (3.3)	0.144
Skeletal muscle area L3 (cm²)	155.5 (31.5)	126.2 (54.6)	170.8 (30.7)	**<0.001**
SMI (mean + SD)	49.6 (10.6)	37.8 (5.6)	54.8 (12.2)	**<0.001**

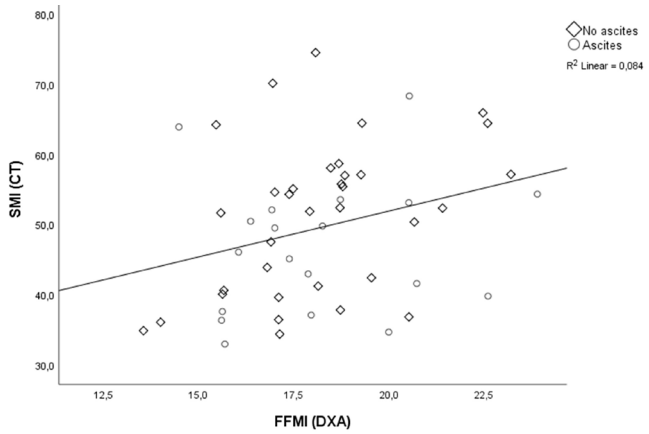
BMI; body mass index, FMI; fat mass index, DXA; dual-energy x-ray absorptiometry, ASMI; appendicular skeletal muscle mass index, SMI; skeletal muscle mass index. Median and inter-quartile range unless otherwise stated. T-test with equal variances not assumed. *Missing data 5 patients, ** Missing data 2 patients

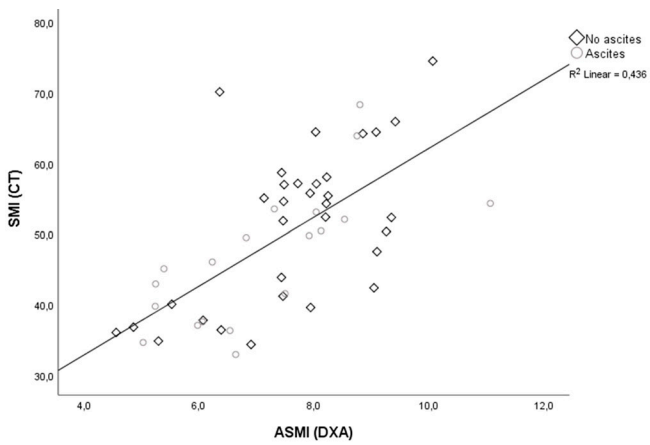
We found a strong inter-method correlation between SMI_{CT} and $ASMI_{DXA}$, and the presence of ascites did not influence the correlation between these measures. FFMI by DXA was not correlated with SMI or ASMI in patients with ascites. Figure 8 shows scatterplots of the relationship between the different measurements according to presences or absence of ascites.

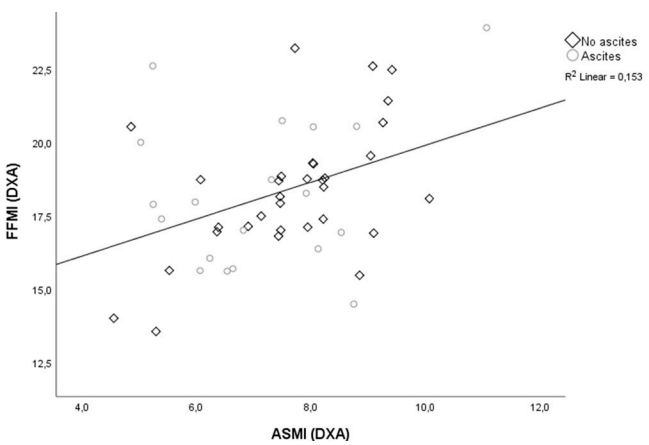
المنارة للاستشارات

ww

Figure 8. Scatterplot of the relationship between SMI_{CT}, $FFMI_{DXA}$, and $ASMI_{DXA}$







ASMI; appendicular skeletal muscle mass index, CT; computed tomography, DXA; dual-energy x-ray absorptiometry, FFMI; fat-free mass index, SMI; skeletal muscle mass index

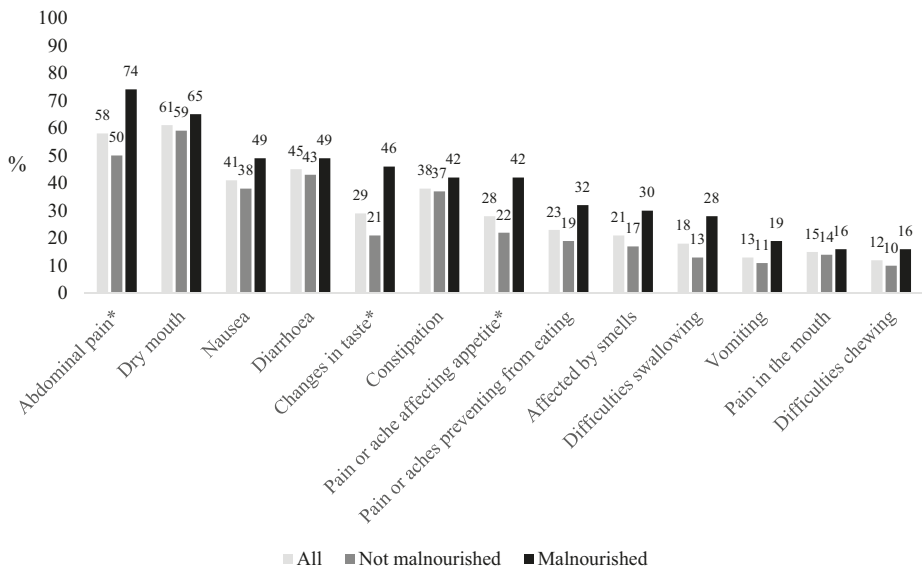
المنارة للاستشارات
ww

6.5 Study III

In total, 133 adult patients with chronic liver disease under evaluation for liver transplantation participated in the study. We found a high prevalence of NIS in patients with chronic liver disease and strong correlations between the frequency of NIS, HRQOL and malnutrition.

Among the included patients, 35% were Child-Pugh A, 48% Child-Pugh B and 17% were Child-Pugh C. The prevalence of different NIS was high and 90 % reported one or more NIS. The most frequently reported symptoms for patients with malnutrition was abdominal pain, dry mouth, nausea, diarrhoea and changes in taste (Figure 9).

Figure 9. Frequency of nutrition impact symptoms assessed by the Eating Symptom Questionnaire related to nutritional status according to the Global Leadership Initiative for Malnutrition criteria.

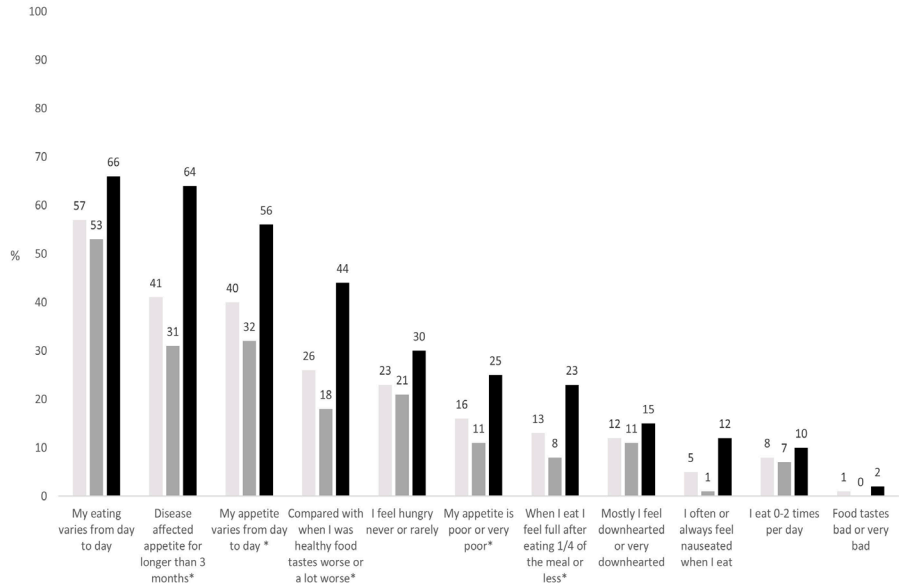


*Statistically significant differences between groups

Sixty seven percent of the patients reported eating two times or less per day and 42% reported that their disease had affected the appetite for more than three months (Figure 10).

المنارة للاستشارات
ww

Figure 10. Frequency of nutrition impact symptoms assessed by the Disease Related Appetite Questionnaire (DRAQ) related to nutritional status according to the GLIM criteria.



*Statistically significant differences between groups

The following NIS were significantly associated with malnutrition according to the GLIM criteria: abdominal pain ($p = 0.033$), pain or ache affecting appetite ($p = 0.034$), changes in taste ($p = 0.004$), poor appetite ($p = 0.010$), varying appetite ($p = 0.010$), early satiety ($p = 0.010$), food tasting worse than when healthy ($p = 0.007$) and for how long the disease had affected the appetite ($p = 0.001$).

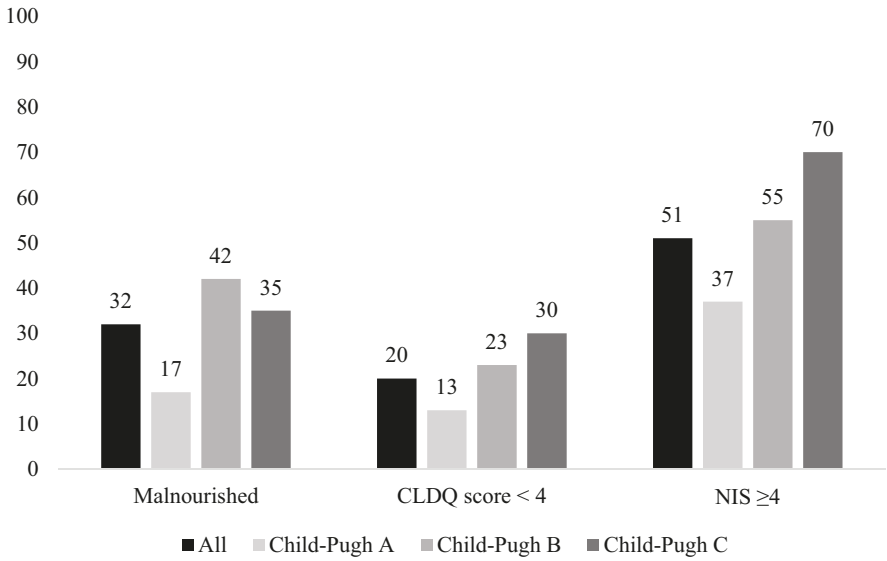
The NIS frequency from the ESQ was strongly negatively correlated with CLDQ (Pearson r -0.717, $p < 0.001$). All quality of life domains were significantly lower in the malnourished group. The median CLDQ in malnourished patients was lower than in well-nourished patients (1 score-point, 95% CI: -1.5, -0.5, p-value < 0.001). After adjusting for gender and Child-Pugh score, the difference in median CLDQ between malnourished patients and well-nourished patients was -0.7 score-point (95% CI: -1.1, -0.3, p-value 0.002).

Low HRQOL and reporting 4 or more NIS was more prevalent in patients with more severe liver disease (Figure 11).

المنارة للاستشارات

ww

Figure 11. Malnutrition, Quality of Life and nutrition impact symptoms according to severity of liver disease (%)

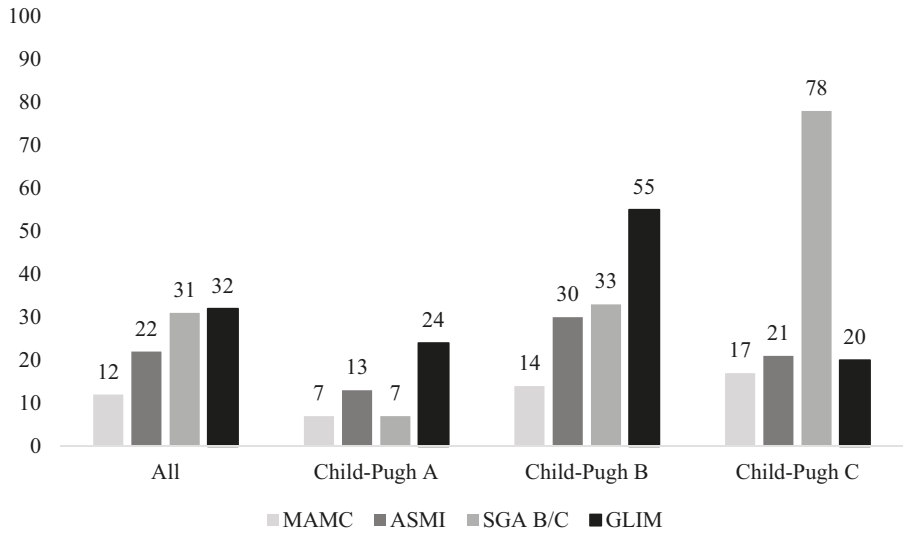


NIS; nutrition impact symptoms, CLDQ; chronic liver disease questionnaire

Malnutrition was present in 32% according to the GLIM criteria with the majority fulfilling the phenotypic criterion reduced muscle mass according to ASMI measured with DXA. The prevalence of low ASMI was 23% and 11% had a MAMC in the lowest percentile. Sixty eight percent were classified as SGA A (well-nourished), 23% as SGA B (suspected or moderately malnourished) and 8% as SGA C (severely malnourished). When comparing between the different Child Pugh groups, low MAMC and SGA B/C were more prevalent in patients with Child Pugh C, and low ASMI and malnutrition according to GLIM was most prevalent in Child Pugh B (Figure 12).

المنارة للاستشارات
ww

Figure 12. Prevalence of malnutrition and muscle mass depletion according to different assessment tools in the different Child-Pugh classes (%)



MAMC; mid-arm muscle circumference, ASMI; appendicular skeletal muscle mass index, SGA; subjective global assessment, GLIM; The Global Leadership Initiative on Malnutrition

6.5.1 Not in the published paper

A sample from the Swedish general population (n=506) filled in the ESQ and DRAQ. This group was a representative sample of the Swedish population between 18-80 years old but was different from patients with chronic liver disease regarding age (in median 46 years) and gender. In this national sample, 77% reported one or more symptoms. The age group 18-24 and 25-29 reported more symptoms than the older age groups. The sample was intended to serve as control group for the chronic liver disease cohort but because of the skewed age and gender distribution compared to the population with chronic liver disease, it was not deemed appropriate to present distribution for each symptom. When comparing the control group from the general population with a multinomial logistic regression, the following symptoms were more frequent in patients with chronic liver disease after adjusting for age: abdominal pain (p=0.002), diarrhoea (p=0.001), dry mouth (p=<0.001), poor appetite (p=<0.001), my appetite varies from day to day (p=0.006), food tastes bad (p=0.008) and my eating varies from day to day (p=0.001).

المنارة للاستشارات

ww

6.6 Study IV

In total, 143 IC measurements performed in median on postoperative day (POD) 6 (IQR 3), were retrospectively analysed. The mean mREE was 1950 ± 461 kcal (range 720-3309 kcal) or 24.5 ± 6.1 kcal/kg body weight. There were significant differences for absolute values in REE between men and women, whereas there was no significant difference in mREE between men and women when adjusted for body weight (24.8 ± 6.1 vs. 23.9 ± 6.2 kcal/kg body weight, p=0.440). Hypermetabolism was present in almost half of the population (49%) and was defined as a mREE >120% of what was predicted with the Harris & Benedict equation.

There was a low accuracy of HB and of fixed factors. The highest accuracy rate in patients with a BMI <25 kg/m² was achieved when the fixed factor 35 kcal/kg (47%) was applied; the HB equation predicted REE accurately (± 10% of mREE) in 18% of these patients. The fixed factor 30 kcal/kg had the highest accuracy rate in patients with BMI 25-29.9 (39%) and the fixed factor 25 kcal/kg (30%) for patients with BMI ≥30.

Bland-Altman analysis between mREE and the prediction of energy expenditure and energy requirement showed wide limits of agreement. The lowest mean differences, -95 kcal, was for the fixed factor 30 kcal/kg body weight, although the 95% CI was between -1268 to 1077 kcal (Table 7).

Table 7. The limits of agreement between the methods: Bland-Altman analysis

Difference for formula, kcal	Mean	SD	-1.96 SD	+1.96 SD
mREE - Harris & Benedict	256	398	-524	1035
mREE x 1.2 – 25 kcal/kg	311	564	-795	1417
mREE x 1.2 – 30 kcal/kg	-95	598	-1268	1077
mREE x 1.2 – 35 kcal/kg	-501	436	-1760	757
mREE – new equation	1.9	349	-682	686

mREE; measured resting energy expenditure, SD; standard deviation, kcal; kilocalories

Concordance between mREE and HB equation and the fixed factors was low (Table 8).

المنارة للاستشارات

Table 8. Concordance between measured resting energy expenditure and predicted resting energy expenditure and fixed factors

Method	CCC	95% CI	r^2
Harrris & Benedict equation	0.350	0.248, 0.445	0.26
25 kcal/kg body weight	0.254	0.130, 0.371	0.11
30 kcal/kg body weight	0.317	0.167, 0.453	0.11
35 kcal/kg body weight	0.231	0.116, 0.339	0.11
New equation	0.605	0.505, 0.689	0.42

CCC; Lin's concordance coefficient, CI; confidence interval, r^2; Pearsons r squared

In a multivariate linear regression, surgery time and male gender increased mREE, while age, MELD score and cold ischemia time decreased mREE (Table 9).

Table 9. Factors independently related to measured resting energy expenditure in multivariate linear regression.

Variable	Coefficient	95% CI	P-value
Age	-10.9	-15.8, -5.9	**<0.001**
Gender	272	76, 468	**0.007**
MELD day 0	-13.9	-24.7, -3.1	**0.012**
Surgery time	1.12	0.33, 1.92	**0.006**
Cold ischemia time	-0.62	-1.08, -0.20	**0.011**

CI: confidence interval; IC: indirect calorimetry; MELD: Model for End-Stage Liver Disease; kg: kilogram

A new equation was derived that included age, gender, body weight on day of IC, surgery time in minutes, cumulative dose of steroids/body weight, cold ischemia time in minutes and MELD score. All variables contributed significantly and accounted for 42 % of the variability observed in mREE. The resulting predictive equation was the following:

REE = 2059.6 + (add 344.7 if male) + (1.3 x surgery time) + (5.4 x weight) – (11.6 x age) – (11.8 x MELD) – (11.6 x cumulative dose of steroids divided by body weight) – (0.7 x cold ischemia time)

المنارة للاستشارات

ww

where surgery time and cold ischemia time are in minutes, weight is body weight (kg), age is in years, MELD score on the day before transplantation (MELD is derived from weighted scores for creatinine, INR and bilirubine), cumulative dose of steroids is intravenous steroids postoperative day 1- 5 divided by body weight. The new equation showed a higher concordance than HB and fixed factors: Lin's concordance correlation (CCC= 0.605, 95 % CI 0.503-0.689) (Table 8).

The low accuracy of HB, the new equation and the fixed factors suggest that REE should be measured with IC early after liver transplantation in order to reduce the risk of both under- and overfeeding individual patients.

المنارة للاستشارات

7 DISCUSSION

7.1 Results discussion

There have been significant advances in nutritional assessment research in patients with chronic liver disease during the years since the studies included in this thesis were designed. CT is now an established body composition measurement method recommended by both EASL and ESPEN to measure muscle mass depletion if a CT scan is available. Still, many methodological questions remain. This thesis has contributed with an understanding of DXAs role in assessment of body composition in chronic liver disease: FFMI is associated with infections after liver transplantation (*Study I*), ASMI measured by DXA is correlated with SMI measured by CT (*Study II*) and identified reduced muscle mass in *Study III*. We found that NIS were prevalent in patients with chronic liver disease and associated with malnutrition and worse HRQOL (*Study III*). REE should be measured after liver transplantation instead of calculating energy requirements to avoid under or overfeeding after liver transplantation (*Study IV*). Some of the results in this thesis warrant further discussion.

7.1.1 Identifying malnutrition and muscle mass depletion

The focus in *Study I-III* was to study malnutrition or muscle mass depletion, although assessment of nutritional status in general was also explored to some extent. In most national guidelines in Sweden, as well as international guidelines on how to screen or diagnose malnutrition, BMI is mentioned (14, 155, 157, 158). EASL recommends to assume that malnutrition is present if BMI is < 18.5 kg/m^2 (39) although such cases were rare in our cohort. In the four studies in this thesis, the prevalence of a BMI below 20 kg/m^2 was only 4-8%. Even so, the prevalence of malnutrition and/or muscle mass depletion was markedly higher indicating that BMI is not useful as a marker of malnutrition in patients with chronic liver disease under liver transplant evaluation. BMI is affected by fluid accumulation and in patients with pronounced ascites and oedema BMI can be falsely high. Sarcopenia was not investigated because of the lack of data on muscle strength or functional parameters. The prevalence of muscle mass depletion in our studies (15-40%, Table 5) was lower compared to those of other studies (68-76%) (23, 35, 110), although it is important to acknowledge differences in severity of liver disease, country of origin and methodology. The large range in prevalence of muscle mass depletion in our studies confirms the results from previous studies where the prevalence is highly dependent on the method used (100).

DXA was used to study body composition even if the method has some limitations, especially in patients with fluid accumulation. The prevalence of patients with malnutrition in *Study I* was lower than reported in *Study II* and *III*. This can

المنارة للاستشارات

ww

be attributed to the use of whole-body composition parameters which may be affected by ascites. Because of the retrospective nature of the study, the analysis of the nutritional assessment by dietitians in *Study I* suffered from methodological problems. Many factors that are normally considered (e.g. dietary intake, anthropometric measurements) were not available.

An assessment of sarcopenia is recommended in patients with cirrhosis by either DXA or CT according to the newly published guidelines by ESPEN and EASL (39, 60). The main aim in *Study II*, was to study inter-method correlations between DXA and CT *Study II* demonstrated that ASMI and SMI are correlated, also in patients with ascites. However, FFMI measured by DXA was not correlated with SMI or ASMI in patients with ascites. This finding suggests that FFMI measured with DXA is not an accurate measurement to determine body composition in patients with ascites but that ASMI can be used.

The GLIM criteria were used to diagnose malnutrition in *Study III* in which 32% of the population was classified as malnourished. The GLIM criteria still need further validation in prospective studies. GLIM is however promising because it includes reduced muscle mass as phenotypic criterion. In patients with ascites and fluid accumulation, weight loss and BMI as phenotypic criterions are not appropriate, and in those patients malnutrition can instead be identified by measuring muscle mass.

7.1.2 Influence of fluid accumulation on nutritional assessment

The main limitation in nutritional assessment of patients with liver cirrhosis or post-transplantation is fluid accumulation, both in the form of ascites and peripheral oedema. In healthy subjects, the average amount of water is 73.2% in the body. In cirrhosis, even in the compensated state, it is common to have an increased amount of extracellular and intracellular water (159). Hydration status has been evaluated in a few studies in patients with cirrhosis. Strauss et al. measured hydration status with isotopic dilution technique and found both sexes to be overhydrated (76.1% in men and 77.6% in women compared to the normal value of 73%), and women were significantly more overhydrated than men (38).

The EASL guidelines recommend adjusting body weight by calculating dry weight and dry BMI if ascites and/or oedema is present (39). It was difficult to account for fluid accumulation in a structured way because of the retrospective nature of *Study I*, *II* and *IV*. This is a limitation in our studies and reflects the difficulties of nutritional assessment in this patient group. Clinicians rarely have the technology to assess fluid accumulation in an accurate way.

المنارة للاستشارات
ww

In *Study II*, ASMI was associated with SMI even in patients with ascites while FFMI was not. Our results suggest that in patients with ascites, ASMI can be used to measure body composition, but FFMI is not recommended. A few studies have evaluated how DXA perform before and after paracentesis in patients with cirrhosis. A small study assessed total body composition, and found that DXA measurement provided a lower lean mass value after paracentesis which was proportional to the amount of drained ascites (160). One study evaluated bone density before and after paracentesis and found no difference in bone density in whole body measurement although there was significant difference in the spine and the hip. The authors suggest that ascites could influence the measurement over the abdomen but not the rest of the body (161). The fluid accumulation in patients with cirrhosis is not only ascites; oedema in the lower limbs is also prevalent. Sinclair et al found that reduced upper limb lean mass was most strongly associated with waiting list mortality compared with total or lower limb lean mass (37) and a possible explanation could be that fluid accumulation in the lower limb gives false results.

The effect of fluid accumulation on CT segmentation has not been accounted for in most previous studies. Overhydration may expand muscle volumes and thereby affect the assessment of sarcopenia, and overhydration was found to significantly affect the measurement of cross-sectional muscle area in a recent study (109).

7.1.3 Gender disparities in chronic liver disease and body composition

The gender distribution in the studies included in this thesis was between 64-74% male and 26-36% female, which is in accordance with most Western countries were women represent approximately 30% of liver transplantation recipients (162). The distribution in our cohorts can to some extent be explained by the high proportion of patients with PSC which in the Nordic countries is the leading indication for liver transplantation (82), PSC is a disease where 2 out of 3 are male. The gender disparities in chronic liver disease are to some extent explored in previous research. The progression of fibrosis in patients with chronic hepatitis C is faster in men compared to women (163). In a Chinese cohort, men were 2.08 times more likely to develop more severe liver disease compared with women (95% CI 1.66-2.61) even after controlling for lifestyle and environmental exposures (164). In an Italian cohort of 12200 patients with chronic liver disease, the male to female ratio was 1.4, although the prevalence of cirrhosis was not different between men and women (21.4% vs 22.2%) (165). In contrast, The National Board of Health and Welfare in Sweden reported that men were 2.5-2.7 times more likely to die from liver cirrhosis than women during the years 1992-2001 (166, 167).

The current understanding of differences in body composition between men and women is still limited. It is important to have nutritional assessment tools that

المنارة للاستشارات

ww

identify all patients at risk, irrespective of gender or ethnicity. We found gender differences in the prevalence of muscle mass depletion and malnutrition in *Study I-II*. In *Study I* there was a marked difference with men having more muscle mass depletion and women more fat depletion, i.e. adipopenia. Our findings are in line with previous reports that the characteristics of tissue loss are different in men and women with cirrhosis, where sarcopenia is more common in men and women more often present with fat depletion (30, 31). Peng et al showed that men lost a higher proportion of their body protein than women, irrespective of disease severity (168). In the Nordic countries, female liver transplant recipients have a 7% lower risk of death than men (hazard ratio 0.93, 95% CI 0.88-0.98) (82). The Nordic results are different from other countries: although the prevalence of muscle mass depletion correlates with post-transplant mortality and muscle mass depletion is higher in male pre-transplant candidate, post-transplant survival is not different between genders (21, 51).

The cause of the different distribution of adipose tissue and muscle mass between men and women is not fully understood. The liver has an important role in sex hormones regulation and alterations in advanced liver disease may play a role. One of the few randomised controlled trials performed to treat sarcopenia was conducted with intramuscular testosterone treatment for 12 months to male patients with cirrhosis. Patients who received testosterone increased their muscle mass (169).

In *Study III* there was a tendency for women to report more NIS than men (p=0.05). No difference was found in prevalence of malnutrition or in HRQOL between men and women. Zambrano et al used the patient-generated SGA to determine malnutrition and found women to be more malnourished than men, although muscle mass depletion measured with CT was more common in men (170). Potential differences in prevalence of malnutrition between genders have not been explored in detail in research, presumably because of the lower frequencies of women with severe liver disease which often make such analyses under-powered.

7.1.4 Outcome after liver transplantation

The result from *Study I* shows that a low FFMI is associated with an increased risk of severe infections within the first post-transplant month. Our results are in accordance with previous research in which severe malnutrition was associated with infections after liver transplantation (171). The most common causes for long term mortality after liver transplantation are malignancy, cardiovascular disease and infection (172).

Length of stay (LOS) is sometimes used as a quality metric (173) and was used as a variable in *Study 1*. We found that post-operative dialysis ($P = 0.004$) and post-operative infections ($P < 0.001$) were significantly associated with LOS in hospital

المنارة للاستشارات

but body composition was not. LOS could be argued to be a financial metric and not a quality metric and is influenced by many factors, although reducing LOS could potentially reduce the risk of in-hospital infections which is beneficial for the patient. When comparing data from our study to others, we speculated that LOS could be affected by differences in health care organisation. Different practises for rehabilitation exist in different centres and countries. In the US it is common for patients to go to rehabilitation facilities while in the UK the patients tend to stay for rehabilitation in the hospital. At our transplant centre, patients from external regions are often discharged to the home hospital while patients from the transplant region either go to rehabilitation facilities or may stay longer at the transplant centre. The parameter LOS does not provide information of resource utilisation after discharge. A short LOS should preferably be weighed against the potentially risk of higher readmission rates. Readmission rates were not analysed in *Study I* or *Study IV*.

Assessment methods that provide information about body composition can be valuable to identify patients at risk of adverse outcomes (171). In a recent meta-analysis of different nutritional assessment tools, the different tools that identified a higher risk of pre-transplant mortality were: TSF risk ratio (RR) 2.15 (95% CI 1.5-3.07), MAMC RR 2.51 (95% CI 1.53-4.1), and CT RR 2.34 (95% CI 1.64-3.36) (11). In the studies included in this thesis, mortality was not analysed because of the high survival rate in our centre, which precluded meaningful statistical analyses.

7.1.5 Nutrition impact symptoms and quality of life

In *Study III*, 90% reported one or more NIS and 51% reported four or more NIS. Malnourished patients reported more NIS. Certain NIS, such as pain, poor appetite, changes in taste and early satiety, were associated with malnutrition. The high prevalence of NIS in patients with chronic liver disease is a unique finding because our study was the first to consider the full spectrum of symptoms that can affect eating. The high prevalence of NIS and the association with malnutrition and HRQOL support the idea that NIS should be routinely assessed in patients with chronic liver diseases. The study does not present causality, although it could be hypothesised that treatment of NIS may work as a preventive action to avoid malnutrition to develop. Previous studies have mainly focused on gastrointestinal symptoms. In a study aimed at identifying patient-perceived to these interventions, patients with Child Pugh B and C liver cirrhosis (174) reported that barriers for an adequate nutritional intake were low energy, pain/illness, nausea/vomiting and ascites . Only 56% had a good appetite and 53% could eat an entire meal. Up to 80 % of patients with liver cirrhosis report one or more gastrointestinal symptoms (175). The most common reported symptoms were abdominal bloating, abdominal pain, belching, diarrhoea and constipation. Gastrointestinal symptoms were

المنارة للاستشارات

ww

associated with recent weight loss and impaired physical and mental health-related quality of life in patients with liver cirrhosis (62).

When planning health care resources, it is important to know the prevalence of adverse outcomes that might need additional resources to prevent or to treat. For an individual patient it might not always be necessary to be exact on whether the patient is suffering from malnutrition, sarcopenia or muscle mass depletion. The important factors could be how the patient is feeling and what affect the disease has on daily life and prognosis.

We examined associations between NIS, malnutrition and HRQOL in *Study III* and found that malnutrition was significantly related to a worse quality of life. The frequency of NIS according to the ESQ was strongly negatively correlated with HRQOL according to CLDQ. Our result are consistent with a previous Swedish study on patients with liver cirrhosis, where gastrointestinal symptoms were associated with recent weight loss and impaired HRQOL (62). The negative impact of malnutrition on HRQOL has been described by several studies (130, 132, 176). There have been few investigations on nutritional interventions and their effect on HRQOL in patients with liver disease. In a study of patient with liver cirrhosis, a late night snack with 200 extra kcal improved general health perceptions, role-emotional and mental health components in a one year long intervention (177). In a 6 month long randomised intervention study on patients with liver cirrhosis, one group received nutritional therapy aiming at 30-35 kcal/kg and 1.0-1.5 gram vegetable protein/kg. The intervention group had a higher increase in HRQOL (106).

Our results in *Study III* highlight the importance of identifying NIS since a high frequency of NIS is a risk factor for low HRQOL. Whether treatment of NIS would also improve HRQOL in patients with liver disease needs to be explored in future research.

The prevalence of NIS in a general population has not been systematically explored before. In our (unpublished) study on 506 statistically representative Swedes, we found that NIS were surprisingly common in the general population. The questionnaires were sent out during the flu season in January and February and we speculate that different viral diseases during the time period may have significantly reflected on our findings. Preferably, the study should be repeated in e.g. early autumn before we draw any further conclusions about the prevalence of NIS in the general population. A previous study of self-reported somatic and psychological symptoms showed that women reported higher total symptom prevalence than men and a trend was found showing an increase in symptom reporting from 1985 and onwards (178). A study aiming at investigating trends in self-reported general health, showed that the risk of having ≥3 symptoms increased significantly from 2000 to 2016 (179). The increases in symptoms were significantly higher

المنارة للاستشارات

in young and individuals with lower education (179). This is in accordance with our observation that the younger population reported more symptoms. Another Swedish study investigated gastrointestinal symptoms in patients with hereditary transthyretin amyloidosis after liver transplantation and compared frequency of symptoms with patients liver transplanted due to end-stage liver disease as well as healthy controls. Symptoms was evaluated with The Gastrointestinal Symptoms Rating Scale. The prevalence of GI symptoms was higher in patients with hereditary transthyretin amyloidosis than in healthy controls but equal to that of transplanted controls (180).

The high frequency of symptoms reported by patients with chronic liver disease suggest a potential to improve patients HRQOL if the symptoms are treated. According to my clinical experience, some symptoms are barriers for implementing nutritional interventions and the results from *Study III* confirms an association with NIS and malnutrition and HRQOL.

7.1.6 Energy requirement after liver transplantation

In the immediate post-transplant phase, it is routine practice at our transplant centre to receive medical nutrition therapy. *Study IV* was designed to increase our understanding of energy expenditure after liver transplantation in order to enable optimal nutritional therapy. Malnutrition and eating difficulties are prevalent in the liver transplant candidate (181) and previous research demonstrated that early enteral nutrition is associated with fewer viral infections (182). Energy supply needs to be balanced towards the patients total energy expenditure (TEE), which includes REE, food-related thermogenesis and energy expenditure related to physical activity (39). A recent study of energy balance demonstrated that 77.8% of measured energy requirement was met between the 7th and 10th day after liver transplantation (183), however only 6.9% had enteral nutrition to support the energy intake. There has been a lot of debate on whether to provide a hypocaloric or isocaloric feed in ICU-patients (184). This has however not been explored in detail in liver transplantation. Kyoung et al advise to provide a lower amount of energy (<18 kcal/kg.BW/d) during the first 48 h postoperatively (185). A reason for the lack of data on how much energy should be supplied during the different phases after liver transplantation could be the scarcity of data on REE in the liver transplant recipient. Earlier studies report conflicting data on REE in patients early after liver transplantation. Two studies on 14 patients and 16 patients showed no significant changes in REE before and after LT (144, 186). However, hypermetabolism before transplantation has been found to be associated with hypermetabolism after liver transplantation in other studies (187, 188). Plank et al showed that REE was significantly elevated after LT with the highest REE on POD 10 in a study on 14 patients with repeated measures of REE before surgery and up to 1 year after liver transplantation (189).

المنارة للاستشارات

ww

In *Study IV*, we found that the HB equation for predicting REE, as well as the fixed factors suggested in the ESPEN and EASL guidelines, provided estimates of energy requirement that were far too inaccurate to be of clinical value. Other studies have demonstrated predictive equations to be within 90–110% of mREE in only 45% patients with cirrhosis (190), and to be correct in around half of hospitalised patients (191). The difficulty to construct a population specific prediction formula has been described in other studies, where a formula for e.g. patients with cirrhosis accounted for 61% of the variation (192). Even if our own attempt to construct a predictive equation had a higher concordance than both HB and the fixed factor in our population, it had a high variability between patients and can therefore not be recommended for clinical use. Studies of predictive equations compared with IC have been performed in other patient populations (193, 194) and the findings from those studies confirm the difficulties in predicting REE.

Our findings in *Study IV* suggest that indirect calorimetry should be used to measure REE early after liver transplantation to prevent under- or overfeeding. It could be argued that it is not feasible to measure REE on all patients. Liver transplantation involves many procedures and significant costs to which IC would add relatively little. It is possible that the benefits from providing adequate amounts of energy to help the patient recover faster would rather be cost-effective. It may in theory reduce the LOS and other complications after the surgery. Previous research shows that early enteral nutrition after liver transplantation gives a lower rate of viral infections (182).

7.2 Methodological considerations

7.2.1 Study design

Studies can be either observational or experimental. The studies in this thesis are observational studies. *Study I, II and IV* are cohort studies. A cohort study is a good study design to explore etiological questions. A cohort is a group of people sharing the same experience, in this case a liver transplantation where time is a parameter. In *Study I* muscle mass was studied before liver transplantation and compared to what happened after the surgery (e.g. the exposure). In *Study IV* the purpose was to measure the prevalence of the "disease" i.e. abnormal metabolism within our cohort. The main limitation in *Study IV* was the lack of baseline REE before surgery which limits the possibility to draw conclusions about causality between different factors associated with liver transplantation and mREE. To reduce this limitation, HB was used for comparison, HB was however developed from a healthy population (58). *Study III* was a cross-sectional study of patients during their pre-transplant evaluation and patients with malnutrition were compared to patients without malnutrition.

المنارة للاستشارات

7.2.2 Generalisability

Several aspects need to be considered regarding generalisability of the results from the four studies in this thesis. The different study cohorts represent heterogenous groups of patients with chronic liver disease and liver cirrhosis with different aetiologies. The populations included in the four studies are somewhat different from other transplant centres in the world. Our population in the different studies consists of 30-51% Child-Pugh A, 39-48 % Child-Pugh B and 17-31% Child-Pugh C and a median MELD score of 11-13. The high proportion of Child-Pugh A patients (for liver transplant cohorts) is explained by many having HCC or PSC as main transplant indication. This is also shown in the high proportion of patients with autoimmune diseases, between 31-40%, which is slightly higher than previously reported in the Nordic Countries (172). Sweden has relatively short waiting times and low wait list mortality, which contributes to many patients without severe decompensation being transplanted. The disease severity in the patient group under investigation needs to be considered, since prevalence of malnutrition and sarcopenia is closely linked to severity of liver disease. In *Study III*, the study cohort consists of patients under evaluation for liver transplantation. All were able to fill in questionnaires, which may result in a selected consenting non-encephalopathic Swedish-speaking sample of patients with chronic liver disease. The results may therefore not be generalised to all patients with chronic liver disease.

The choice of different cut-offs in the studies is a consequence of the evolving field of body composition research. It is important to acknowledge this aspect when generalising our results to other populations. The cut-offs of below 5th percentile was used for FFMI in *Study I* and below 10th percentile in *Study II*. The data analysis for *Study I* was performed in 2013-2014 while the analysis for *Study II* was done 2016-2017. In 2015 the ESPEN guideline for Diagnostic criteria for Malnutrition (155) was published, where non-age adjusted cut-offs for FFMI were suggested. The 10th percentile cut-off in *Study II* was chosen because it was more similar to the cut-offs suggested in the ESPEN guideline. Muscle mass varies across the lifetime and is generally decreasing with age. The EWGSOP therefore recommend the use of normative references (healthy young adults) whenever possible, with cut-offs set at −2 standard deviations compared to the mean reference value (17). In contrast to these recommendations, no age-adjusted cut-offs are available for SMI. To enable comparisons with other populations, the cut-offs suggested by EWGSOP and GLIM were used for ASMI in S*tudy III* even though they are not age adjusted. The varying prevalence of malnutrition and muscle mass depletion in the different studies in this thesis reflect the difficulties in the field of nutritional assessment. There is little recently published data on healthy individual´s body composition and there is a lack of Nordic reference data. Sweden had an increased immigration in this millennium, which also reflects on liver transplantation cohorts. A recent study showed that immigration increased the incidence

المنارة للاستشارات

ww

of HCC and the need for active treatment such as liver transplantation in Sweden (195). Body composition varies in different parts of the world. Ethnicity should therefore be considered when choosing cut-offs for low muscle mass or fat mass. It could be argued that it is not always relevant to compare patients with chronic diseases with healthy individuals. Comparisons should rather be done with the ideal body reserves that are needed to withstand the consequences of the disease or interventions (e.g. transplantation). This approach was used in *Study I* where FFMI and FMI were analysed as continuous variables in the multivariate analysis.

7.2.3 Aspects that may affect validity

Systematic errors such as selection bias, information bias and confounding can affect results. Bias creates associations that are not true, and confounding describes an association that is true, but the interpretation of the association is wrong (196). The low number of women in the four studies affects the gender-specific statistical calculations, which in turn could affect the external validity. However, this reflects liver transplant populations in general in which the male gender is over-represented (162).

7.2.3.1 Validity in data sources

The different data sources in this thesis have different advantages and disadvantages, as shown in Table 1. Manufacturers of DXA machines have developed different models and software versions which need to be considered when comparing validity of body composition measurements (28). A limitation in *Study II* is the use of CT scans performed for clinical purposes, both contrast enhanced scans and unenhanced scans. Previous research has shown that SMI is increased by up to 2.8% with the use of contrast medium (197, 198). CT scans performed with different tube voltages have also been included in this thesis, both 100 kV and 120 kV. It is unknown to what degree this may have affected the results. In a study comparing scans with 80 kV and 140 kV, SMI was 5.2% lower with 80 kV (199). There are also several different software programs in use for CT segmentation. In *Study II* Image J was used. Most studies on patients with cirrhosis use the software program SliceOmatic. A comparison of segmentation using different programs has however shown excellent agreement between different software (200). Our use of Image J should therefore not preclude comparisons of our results with those from other studies.

Data from questionnaires are self-reported and include some limitations, such as the uncertainty about how the participant interpreted the questions. The group which developed the questionnaires ESQ and DRAQ (70) explored the patients interpretations of the questions during the development process in order to limit the risk of individuals interpreting the questions in different ways. The use of information collected from medical charts may provide inaccurate information

المنارة للاستشارات

because medical personal could have mis-recorded information. Data quality includes uncertainty in data accuracy, completeness, consistency, credibility, and timeliness (201). These potential limitations have to some extant been dealt with in the statistical analysis from using multivariate analysis when possible.

7.2.3.2 Selection bias

Selection bias can arise when there are differences in groups regarding how they were included in the study. In *Study I-II*, the study population consists of patients with a DXA measurement performed at Karolinska University Hospital during the liver transplantation evaluation. There is a theoretical risk of selection bias, in that the patients with a DXA done elsewhere could potentially have differed in muscle mass compared to the patients who had a DXA scan performed at Karolinska University Hospital. *Study II* has a higher proportion of HCC than some other liver transplant cohorts. It is more common for patients with HCC to have a CT at our centre, which potentially could affect the prevalence of muscle mass depletion. It is, however, unlikely that it affected the main aim of the study which was to perform inter-method comparisons between DXA and CT. In *Study III* there is a risk of selection bias if patients reporting NIS could be more inclined to participate in a study that investigates their current problems. In *Study IV*, patients with certain characteristics were included, e.g. the healthier subjects that were able to have the IC measurement. Also, the staff at the ward were not able to perform a measurement when the workload was heavy which could influence the selection of patients. The cohort is not representative of all liver transplanted patients. That the results from this study will only be generalisable to certain patients after a liver transplantation was clearly stated in *Study IV.*

7.2.3.3 Information bias

Misclassification can occur from systematic errors of the study variable measured (196), for example if participants are classified as malnourished or not malnourished. The misclassification can be differential where there is different misclassification between groups or non-differential where the misclassification is equal between groups. To overcome the uncertainty involved in the retrospective analysis in *Study I*, any weight loss over 10% in combination with eating difficulties was used to define malnutrition, since it was not always clear if the weight loss was voluntary or involuntary. To avoid misclassifying patients as malnourished when they were not, a strict definition was used. This instead involves a risk of some patients being stratified as "at risk of malnutrition" when other criteria could have stratified them as malnourished. In *Study III*, there is a low risk of non-differential misclassification (between the groups malnourished and not-malnourished patients), since weight loss had to be recalled from the patient if no earlier weight was available in the medical chart. The influence of ascites on weight also introduces a risk of misclassification.

المنارة للاستشارات

ww

7.2.3.4 Confounding

A confounder is a parameter that is associated with both the exposure and the outcome, but the association is not in the causal pathway (196). Adjustments for potential confounders were made within the statistical analyses and the confounders were adjusted based on previous knowledge from the literature as well as on clinical experience. In *Study I*, the logistic regression model for the outcome variable post-operative infections was adjusted for many variables including age, sex, body composition and different pre and post liver transplantation parameters. In *Study II*, inter-method correlation was tested in both patients with and without ascites. In the multinomial logistic regression analysis in *Study III*, we adjusted for sex, Child-Pugh class, and ascites, which are potential confounders. In *Study IV*, a multiple linear regression analysis was performed to test if transplantation specific factors affected REE. Also, the previously known factors weight, height, age and gender were included in the regression analysis to clarify how much these known confounders contributed to REE. However, the potential risk of unmeasured and unknown confounders cannot be fully disregarded in the four studies in this thesis.

المنارة للاستشارات

8 CONCLUSIONS AND CLINICAL IMPLICATIONS

In this thesis, different aspects of nutritional assessment in patients undergoing liver transplantation evaluation and liver transplantation have been described and analysed. From the studies included in this thesis, we conclude that:

Body composition should be assessed during pre-transplant evaluation

- FFMI is associated with infections early after liver transplantation
- When assessing body composition, ASMI by DXA or SMI by CT are preferable
- The proportion of muscle mass depletion varies with assessment method and gender

NIS should be routinely assessed in patients with chronic liver diseases

- NIS are common in patients with chronic liver disease and patients with multiple symptoms are more likely to be malnourished and have worse quality of life
- Certain symptoms, such as pain, poor appetite, change in taste and early satiety are associated with malnutrition

Indirect calorimetry to measure energy expenditure is recommended for estimating energy requirements after liver transplantation

- Resting energy expenditure is often increased early after liver transplantation
- Estimates of energy expenditure were inaccurate in most cases when compared to measured energy expenditure

In clinical practise many different factors, such as accessibility to body composition technology as well as economical and organisational resources, affect the possibilities to implement the above recommendations. NIS can be screened for in a quick and cost-effective way, for example by sending the patients questionnaires before the visit. More resource is needed in order to treat identified symptoms. When it comes to assessing body composition and resting energy expenditure, my personal conclusion from completing my PhD-studies is something that far more renowned persons have said before me: "The more I learn, the more *I realise how much I don't* know". What I do know, is that nutritional assessment in patients with liver disease is important, muscle mass should be objectively measured and there is still much to learn.

المنارة للاستشارات

ww

9 FUTURE PERSPECTIVES

Many new questions have arisen during the completion of the four studies and the writing of this thesis. Some specific areas of interest are:

- CT to measure muscle mass in patients with chronic liver disease is now an established method in research. It is unlikely that the majority of transplant centres around the world will have resources to perform repeated CT measurements. There is still little knowledge on how much exercise and how long of a period of improved nutrition is needed to increase muscle mass. I would like to design a study to explore how muscle mass depletion evolves during the progression of the liver disease and in conjuction with nutrition therapy. There is a need for intervention studies to explore how long it takes to increase muscle mass and whether CT and/or more clinically available methods such as hand grip strength measurements are reliable ways to measure the increase.
- With the results from *Study III*, we hypothesise that early identification and treatment of NIS can prevent malnutrition and improve HRQOL. An interventional longitudinal study could test this hypothesis. I would like to conduct a prospective study of how NIS evolve during different phases of liver disease; at diagnosis of chronic liver disease, in cirrhosis and when decompensation develops.
- Even if I did not explore this specifically, the results in *Study IV* suggest that energy requirements in patients with PSC are different from other patients with chronic liver disease. I would like to investigate whether this observation is explained by the PSC liver disease or by other factors such as as age, muscle mass or comorobidity such as inflammatory bowel disease.
- We are just beginning to understand how liver cirrhosis and sex hormones affect the body composition of men and women. Further exploration of gender differences in body composition is warranted. Do we need gender-specific assessment tools in addition to gender-specific cut-offs?
- Most of all I want to ask patients about what matters to them. This thesis was built on my frustrations as a dietitian. I am certain that my patients would choose different areas to study. Body composition is important in order to identify patients at risk of adverse outcome, and survival is important for people with life-threatning diseases. HRQOL has not received enough attention in research. What do the patients want?

المنارة للاستشارات
ww

10 POPULÄRVETENSKAPLIG SAMMANFATTNING

Levercirros är en sjukdom som kan ge många olika typer av symtom. Det är vanligt att aptiten är nedsatt när man är sjuk och det kan då vara svårt att äta tillräckligt av alla näringsämnen som kroppen behöver. Levern har en viktig funktion i vår ämnesomsättning både när det gäller fett, protein och kolhydrater samt vitaminer och mineraler. En del av den energi vi får i oss när vi äter lagras i muskler och i levern i form av glykogen. Energin från maten vi äter varar bara i några timmar, efter det används den lagrade energin i levern som energikälla fram till nästa måltid. Vid svår leversjukdom kan inte levern lagra lika mycket energi. Om levern töms på energi och det är långt till nästa måltid behöver kroppen hitta en alternativ energikälla: fettväv och muskelmassa börjar brytas ned. På grund av dessa svårigheter är det vanligt med undernäring hos personer med svår leversjukdom.

Det är också vanligt att samla på sig vätska i buken, ascites, och ödem i benen. Det leder till att vanliga sätt att mäta nutritionsstatus som viktförändring och BMI kan ge felaktiga resultat då en viktförändring kan orsakas av förändringar i vätskemängd och inte i faktisk kroppsmassa. Olika typer av vävnad förbrukar olika mängd energi. Muskelmassa förbrukar t. ex. mer energi än fettmassa och teoretiskt förbrukar inte vatten någon energi. Problemet med ansamlad vätska är också vanligt i det tidiga skedet efter en levertransplantation vilket påverkar möjligheten att korrekt kunna räkna ut energibehovet.

För att bättre kunna bedöma vilka patienter som är undernärda var ett syfte med denna avhandling att studera muskelmassa mätt med olika röntgenmetoder. Ett annat var att studera hur vanligt det är med symtom som påverkar förmågan att äta samt om dessa symtom är associerade med undernäring och livskvalitet. Ytterligare ett syfte var att jämföra uppmätt energibehov med olika sätt att räkna ut energibehov efter en levertransplantation.

I *delstudie I* studerade vi 109 patienter innan och efter en levertransplantation och fann att 2–20 % av patienterna var undernärda när de utreddes för transplantation. Förekomsten varierade beroende på kön och mätmetod. Mätt med dual energy x-ray absorptiometry (DXA) hade 20 % av männen och hos 5 % av kvinnorna en låg fettfri massa och bedömdes därmed som undernärda. Trettiofem (37 %) patienter utvecklade allvarliga infektioner inom 1 månad efter levertransplantation. Vi fann ett samband mellan mängd fettfri massa och förekomst av infektioner. Kroppsammansättning uppmätt med DXA under transplantationsutredningen ger värdefull information om nutritionsstatus hos patienter med levercirros.

المنارة للاستشارات

ww

I *delstudie II* jämförde vi kroppssammansättningsmätningar gjorda med DXA och med datortomografi (DT) under levertransplantationsutredningen hos 53 patienter. Tre olika mätningar jämfördes, fettfri masse index (helkropp) (FFMI) och appendikulärt (muskler i armar och ben) skelettmasseindex (ASMI) från DXA och skelettmuskelmasseindex (SMI) mätt från DT. Nedsatt mängd muskelmassa hittades hos 45 % (SMI), 38 % (ASMI) och 30 % (FFMI) hos patienterna. När de olika metoderna jämfördes var likheten i mätresultatet starkast mellan ASMI och SMI. Hos kvinnor varierade förekomsten av nedsatt mängd muskelmassa från 13 % till 50 % beroende på metod medan förekomsten var relativt lika mellan metoderna hos män, mellan 38 % och 43 %. ASMI mätt med DXA är ett bra och kostnadseffektivt mått för att mäta muskelmassa när DT inte finns tillgängligt hos levertransplantationskandidater.

I *delstudie III* studerades förekomst av symtom som kan påverka ätande hos 133 patienter som utreddes för levertransplantation. Vi undersökte också om det fanns samband mellan symtom och undernäring och livskvalitet. Symtom som kan påverka ätande visade sig vara mycket vanligt: 90 % rapporterade ett eller flera symtom och 51 % rapporterade fyra eller fler symtom. De vanligaste symtomen var muntorrhet (61 %), buksmärta (58 %), diarré (45 %) och illamående (41 %). Trettiotvå procent var undernärda. Patienter med undernäring rapporterade fler symtom och ju fler symtom desto lägre hälsorelaterad livskvalitet. Vissa symtom som smärta, nedsatt aptit, smakförändringar och tidig mättnadskänsla var associerade med förekomst av undernäring.

I den sista studien, *delstudie IV*, studerades energibehov tidigt efter levertransplantation. Olika riktlinjer rekommenderar olika sätt att räkna ut energibehov och beroende på vilken formel som används kan resultatet skilja sig åt. Det är viktigt att veta vilket energibehov en patient har efter levertransplantation för att kunna ordinera rätt mängd näring. För lite näring kan ge sämre läkningsförmåga och ökad risk för infektioner, för mycket näring kan stressa kroppen. Vi fann att det var en stor variation i uppmätt energibehov mellan olika individer. När det uppmätta energibehovet jämfördes med olika formler visade sig att formlerna inte var så bra på att förutspå energibehovet. Patienter med lång operationstid hade högre energibehov under återhämtningsperioden.

Sammanfattningsvis visar resultatet från denna avhandling att andelen individer som bedöms som undernärda eller har nedsatt mängd muskelmassa varierar beroende på vilken metod som används, symtom som kan påverka ätande är mycket vanligt och energibehov bör mätas och inte uppskattas efter levertransplantation.

المنارة للاستشارات
ww

11 ACKNOWLEDGEMENTS

Research is like picking chanterelles. Sometimes all you can see is trees and moss and it feels like you will never find what you are looking for. But then, after walking in the forest for hours you suddenly see some bits of golden mushrooms buried below some sticks and old leaves. My time as a PhD-student felt like a very long walk, thankfully I had good company on the way. I would not be here if it was not for this village of helpful people lifting me higher than I could climb by myself. I would especially like to thank:

Staffan Wahlin, my main supervisor, for your enthusiasm and for always listening, for all the years of encouragement and believing in me. I always left from our meetings feeling refilled with energy. I am forever grateful for your guidance into the world of research.

Ammar Majeed, my co-supervisor, for your help with statistics and reminding me to focus and not taking on too many extra commitments.

Frode Slinde, my co-supervisor, for always taking your time for a quick reply and helping me with all the nutritional questions in my studies.

Gerd Faxén-Irving, my mentor, for encouraging me to become a researcher, for your support, and for teaching me how important it is with participating in rounds to achieve a good collaboration with doctors and nurses at the ward.

My co-authors, **Torkel Brismar**, for introducing me to the world of radiology, **Matteo Bottai**, for your patience and pedagogic approach while helping me with statistics, **Peter Nordstedt**, for all the hard work and continuous strive to improve the care for our patients and for collecting data in study IV, **Greg Nowak**, for your cheerfulness, valuable input and critical thinking.

Annika Bergquist, for being an excellent leader, for believing in the dietitian's value at the Centre for Digestive Disease, for all the inspiration and for being my role-model both as a clinician and researcher.

Per Stål and Hannes Hagström, for giving me the opportunity to participate in a randomised controlled trial and for being my unofficial extra supervisors in the MILES research group.

Magnus Holmer and Pia Loqvist, for the collaboration and fun chats in the TREND-study which helped me keep perspective that there are other things in the liver world than malnutrition.

MILES and PSC research groups, thank you for your friendship and stimulating research discussions.

المنارة للاستشارات

ww

Antti Oksanen, Karouk Said, Anna Abrahamsson, Ammar Barakat, my dear hepatologist friends. For welcoming me into the liver family with open arms. Without your friendliness and curiosity, I would not have stayed. I truly appreciate all the lively discussions in order to improve the care for our patients.

Annika Roback, for answering all my emails within 30 seconds. I admire your organisational skills.

My dear friends and fellow research dietitians, there are no words to describe how much you meant for me during my PhD, **Evelina Liljeberg**, for giving me the idea to look at the DXA measurements, and for all your invaluable input on all my studies, life and everything. **Jessica Ericson**, for teaching me all there is to know about nutrition in surgery and for sharing laughs and tears during all these years.

Kerstin Belqaid, for inspiration and the support throughout my process of becoming an adult researcher.

Ylva Orrevall, for all our terminology discussions even though I did not use to acknowledge the importance of terminology.

Ella Veidemann, my clinical manager for cheering me on and accepting my disappearance from the clinics, I appreciate our good cooperation.

Elisabet Lundström and Lotta Klinge Härberg, my present and previous manager, thank you for allowing me to combine my work with a doctoral education.

All the staff at the **Transplantation clinic**, the **Hepatology clinic** and the **Osteoporosis department**. A special thank you to all nurses who have helped me with collecting information.

Åsa Wilén, Anna Kingfors and Sanna Elfving, my dear friends, former colleagues and fellow foodies. Thank you for all the nice dinners and pep talk to help me fulfil my goals between our meetups.

All my **present and previous dietitian colleagues** at Karolinska University Hospital for all your friendliness, laughs and encouragement.

Helena Frisk, for listening and taking my mind of research while eating dinners, enjoying theatres and hikes. And thanks for all the fun cat memes and videos.

All my friends, thank you for supporting me, for the food and awesome company during my short escapes out in the real world.

Min älskade familj, **Pernilla, Sofia, Jonas och Madde**, tack för att ni stöttar mig och alltid finns där. **Owe och Margareta**, mina kära föräldrar, ni har uppfostrat mig till att tro att jag kan uppnå vad jag vill så länge jag jobbar för det. Bättre föräldrar kan inget barn önska sig.

Keith "was or were", my rock and beloved partner, I could not have stayed sane without your support, all the food, coffee and for doing all the washing up. I love you.

المنارة للاستشارات

ww

12 REFERENCES

1. Swan WI, Vivanti A, Hakel-Smith NA, Hotson B, Orrevall Y, Trostler N, et al. Nutrition Care Process and Model Update: Toward Realizing People-Centered Care and Outcomes Management. Journal of the Academy of Nutrition and Dietetics. 2017;117(12):2003-14.

2. Ljungqvist O, van Gossum A, Sanz ML, de Man F. The European fight against malnutrition. Clinical nutrition (Edinburgh, Scotland). 2010;29(2):149-50.

3. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clinical nutrition (Edinburgh, Scotland). 2008;27(1):5-15.

4. Norman K, Kirchner H, Lochs H, Pirlich M. Malnutrition affects quality of life in gastroenterology patients. World journal of gastroenterology : WJG. 2006;12(21):3380-5.

5. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clinical nutrition (Edinburgh, Scotland). 2003;22(3):235-9.

6. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN Journal of parenteral and enteral nutrition. 1987;11(1):8-13.

7. Merli M, Giusto M, Gentili F, Novelli G, Ferretti G, Riggio O, et al. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. Liver international : official journal of the International Association for the Study of the Liver. 2010;30(2):208-14.

8. Ferreira LG, Anastacio LR, Correia MI. The impact of nutrition on cirrhotic patients awaiting liver transplantation. Current opinion in clinical nutrition and metabolic care. 2010;13(5):554-61.

9. Marr KJ, Shaheen AA, Lam L, Stapleton M, Burak K, Raman M. Nutritional status and the performance of multiple bedside tools for nutrition assessment among patients waiting for liver transplantation: A Canadian experience. Clinical nutrition ESPEN. 2017;17:68-74.

10. Borhofen SM, Gerner C, Lehmann J, Fimmers R, Gortzen J, Hey B, et al. The Royal Free Hospital-Nutritional Prioritizing Tool Is an Independent Predictor of Deterioration of Liver Function and Survival in Cirrhosis. Digestive diseases and sciences. 2016;61(6):1735-43.

11. Ney M, Li S, Vandermeer B, Gramlich L, Ismond KP, Raman M, et al. Systematic review with meta-analysis: Nutritional screening and assessment tools in cirrhosis. Liver international : official journal of the International Association for the Study of the Liver. 2019.

المنارة للاستشارات

ww

12. Amodio P, Bemeur C, Butterworth R, Cordoba J, Kato A, Montagnese S, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. Hepatology (Baltimore, Md). 2013;58(1):325-36.

13. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clinical nutrition (Edinburgh, Scotland). 2016.

14. White JV, Guenter P, Jensen G, Malone A, Schofield M, Academy Malnutrition Work G, et al. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN Journal of parenteral and enteral nutrition. 2012;36(3):275-83.

15. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clinical nutrition (Edinburgh, Scotland). 2019;38(1):1-9.

16. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol (1985). 2000;89(1):81-8.

17. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age and ageing. 2019;48(1):16-31.

18. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing. 2010;39(4):412-23.

19. Schaap LA, Koster A, Visser M. Adiposity, muscle mass, and muscle strength in relation to functional decline in older persons. Epidemiol Rev. 2013;35(1):51-65.

20. Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2017;23(5):625-33.

21. Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. Journal of cachexia, sarcopenia and muscle. 2016;7(2):126-35.

المنارة للاستشارات

22. Jeon JY, Wang HJ, Ock SY, Xu W, Lee JD, Lee JH, et al. Newly Developed Sarcopenia as a Prognostic Factor for Survival in Patients who Underwent Liver Transplantation. PloS one. 2015;10(11):e0143966.

23. Hanai T, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, et al. Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition (Burbank, Los Angeles County, Calif). 2015;31(1):193-9.

24. Bosy-Westphal A, Muller MJ. Identification of skeletal muscle mass depletion across age and BMI groups in health and disease--there is need for a unified definition. Int J Obes (Lond). 2015;39(3):379-86.

25. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology (Baltimore, Md). 2017;66(2):564-74.

26. van Vugt JL, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, JN IJ. Systematic Review and Meta-Analysis of the Impact of Computed Tomography-Assessed Skeletal Muscle Mass on Outcome in Patients Awaiting or Undergoing Liver Transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2016;16(8):2277-92.

27. Lai JC, Sonnenday CJ, Tapper EB, Duarte-Rojo A, Dunn MA, Bernal W, et al. Frailty in liver transplantation: An expert opinion statement from the American Society of Transplantation Liver and Intestinal Community of Practice. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2019;19(7):1896-906.

28. Heymsfield SB, Lohman TG, Wang Z, Going SB. Human body composition. 2 nd ed: Human Kinetics; 2005.

29. Calmet F, Martin P, Pearlman M. Nutrition in Patients With Cirrhosis. Gastroenterol Hepatol (N Y). 2019;15(5):248-54.

30. Nutritional status in cirrhosis. Italian Multicentre Cooperative Project on Nutrition in Liver Cirrhosis. Journal of hepatology. 1994;21(3):317-25.

31. Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, et al. Nutrition and survival in patients with liver cirrhosis. Nutrition (Burbank, Los Angeles County, Calif). 2001;17(6):445-50.

32. Ebadi M, Tandon P, Moctezuma-Velazquez C, Ghosh S, Baracos VE, Mazurak VC, et al. Low subcutaneous adiposity associates with higher mortality in female patients with cirrhosis. Journal of hepatology. 2018;69(3):608-16.

المنارة للاستشارات

ww

33. Rodrigues SG, Brabandt B, Stirnimann G, Maurer MH, Berzigotti A. Adipopenia correlates with higher portal pressure in patients with cirrhosis. Liver international : official journal of the International Association for the Study of the Liver. 2019;39(9):1672-81.

34. Fuller NJ, Jebb SA, Goldberg GR, Pullicino E, Adams C, Cole TJ, et al. Inter-observer variability in the measurement of body composition. European journal of clinical nutrition. 1991;45(1):43-9.

35. Giusto M, Lattanzi B, Albanese C, Galtieri A, Farcomeni A, Giannelli V, et al. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. Eur J Gastroenterol Hepatol. 2015;27(3):328-34.

36. Belarmino G, Gonzalez MC, Sala P, Torrinhas RS, Andraus W, D'Albuquerque LAC, et al. Diagnosing Sarcopenia in Male Patients With Cirrhosis by Dual-Energy X-Ray Absorptiometry Estimates of Appendicular Skeletal Muscle Mass. JPEN Journal of parenteral and enteral nutrition. 2018;42(1):24-36.

37. Sinclair M, Hoermann R, Peterson A, Testro A, Angus PW, Hey P, et al. Use of Dual X-ray Absorptiometry in men with advanced cirrhosis to predict sarcopenia-associated mortality risk. Liver international : official journal of the International Association for the Study of the Liver. 2019;39(6):1089-97.

38. Strauss BJ, Gibson PR, Stroud DB, Borovnicar DJ, Xiong DW, Keogh J. Total body dual X-ray absorptiometry is a good measure of both fat mass and fat-free mass in liver cirrhosis compared to "gold-standard" techniques. Melbourne Liver Group. Annals of the New York Academy of Sciences. 2000;904:55-62.

39. Merli M, Berzigotti A, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L, et al. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. Journal of hepatology. 2019;70(1):172-93.

40. Albanese CV, Diessel E, Genant HK. Clinical applications of body composition measurements using DXA. Journal of Clinical Densitometry. 2003;6(2):75-85.

41. Woodrow G. Body composition analysis techniques in the aged adult: indications and limitations. Current opinion in clinical nutrition and metabolic care. 2009;12(1):8-14.

42. Di Sebastiano KM, Mourtzakis M. A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2012;37(5):811-21.

المنارة للاستشارات

43. Heyward VH, Wagner DR. Applied body composition assessment. 2nd ed. ed: Human Kinetics; 2004.

44. Wells JC, Fewtrell MS. Measuring body composition. Archives of disease in childhood. 2006;91(7):612-7.

45. Lee SY, Gallagher D. Assessment methods in human body composition. Current opinion in clinical nutrition and metabolic care. 2008;11(5):566-72.

46. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. The American journal of physiology. 1996;271(6 Pt 1):E941-51.

47. Elia M, Stratton R, Stubbs J. Techniques for the study of energy balance in man. The Proceedings of the Nutrition Society. 2003;62(2):529-37.

48. Andreoli A, Scalzo G, Masala S, Tarantino U, Guglielmi G. Body composition assessment by dual-energy X-ray absorptiometry (DXA). La Radiologia medica. 2009;114(2):286-300.

49. Heymsfield SB, Gallagher D, Visser M, Nunez C, Wang ZM. Measurement of skeletal muscle: laboratory and epidemiological methods. The journals of gerontology Series A, Biological sciences and medical sciences. 1995;50 Spec No:23-9.

50. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. The Lancet Oncology. 2008;9(7):629-35.

51. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. Journal of the American College of Surgeons. 2010;211(2):271-8.

52. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47.

53. Oshima T, Berger MM, De Waele E, Guttormsen AB, Heidegger CP, Hiesmayr M, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clinical nutrition (Edinburgh, Scotland). 2017;36(3):651-62.

المنارة للاستشارات

ww

54. Heymsfield SB, Thomas DM, Bosy-Westphal A, Muller MJ. The anatomy of resting energy expenditure: body composition mechanisms. European journal of clinical nutrition. 2019;73(2):166-71.

55. Ferreira LG, Santos LF, Anastacio LR, Lima AS, Correia M. Resting Energy Expenditure, Body Composition, and Dietary Intake: A Longitudinal Study Before and After Liver Transplantation. Transplantation. 2013;96(6):579-85.

56. Chen Y, Kintner J, Rifkin SK, Keim KS, Tangney CC. Changes in Resting Energy Expenditure Following Orthotopic Liver Transplantation. JPEN Journal of parenteral and enteral nutrition. 2015.

57. Plauth M, Merli M, Kondrup J, Weimann A, Ferenci P, Muller MJ. ESPEN guidelines for nutrition in liver disease and transplantation. Clinical nutrition (Edinburgh, Scotland). 1997;16(2):43-55.

58. Roza AM, Shizgal HM. The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. The American journal of clinical nutrition. 1984;40(1):168-82.

59. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clinical nutrition (Edinburgh, Scotland). 2017;36(3):623-50.

60. Plauth M, Bernal W, Dasarathy S, Merli M, Plank LD, Schutz T, et al. ESPEN guideline on clinical nutrition in liver disease. Clinical nutrition (Edinburgh, Scotland). 2019.

61. Kubrak C, Olson K, Jha N, Jensen L, McCargar L, Seikaly H, et al. Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. Head & neck. 2010;32(3):290-300.

62. Kalaitzakis E, Simren M, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, et al. Gastrointestinal symptoms in patients with liver cirrhosis: associations with nutritional status and health-related quality of life. Scandinavian journal of gastroenterology. 2006;41(12):1464-72.

63. Aqel BA, Scolapio JS, Dickson RC, Burton DD, Bouras EP. Contribution of ascites to impaired gastric function and nutritional intake in patients with cirrhosis and ascites. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2005;3(11):1095-100.

64. Plauth M, Schutz ET. Cachexia in liver cirrhosis. International journal of cardiology. 2002;85(1):83-7.

المنارة للاستشارات

ww

65. Farhangfar A, Makarewicz M, Ghosh S, Jha N, Scrimger R, Gramlich L, et al. Nutrition impact symptoms in a population cohort of head and neck cancer patients: multivariate regression analysis of symptoms on oral intake, weight loss and survival. Oral oncology. 2014;50(9):877-83.

66. Tong H, Isenring E, Yates P. The prevalence of nutrition impact symptoms and their relationship to quality of life and clinical outcomes in medical oncology patients. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2009;17(1):83-90.

67. Omlin A, Blum D, Wierecky J, Haile SR, Ottery FD, Strasser F. Nutrition impact symptoms in advanced cancer patients: frequency and specific interventions, a case-control study. Journal of cachexia, sarcopenia and muscle. 2013;4(1):55-61.

68. Knudsen AW, Naver A, Bisgaard K, Nordgaard-Lassen I, Becker U, Krag A, et al. Nutrition impact symptoms, handgrip strength and nutritional risk in hospitalized patients with gastroenterological and liver diseases. Scandinavian journal of gastroenterology. 2015;50(10):1191-8.

69. Campbell KL, Bauer JD, Ikehiro A, Johnson DW. Role of nutrition impact symptoms in predicting nutritional status and clinical outcome in hemodialysis patients: a potential screening tool. Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation. 2013;23(4):302-7.

70. Norden J, Gronberg AM, Bosaeus I, Forslund HB, Hulthen L, Rothenberg E, et al. Nutrition impact symptoms and body composition in patients with COPD. European journal of clinical nutrition. 2015;69(2):256-61.

71. Walter SA, Kjellstrom L, Nyhlin H, Talley NJ, Agreus L. Assessment of normal bowel habits in the general adult population: the Popcol study. Scandinavian journal of gastroenterology. 2010;45(5):556-66.

72. Hammerlid E, Adnan A, Silander E. Population-based reference values for the European Organization for Research and Treatment of Cancer Head and Neck module. Head & neck. 2017;39(10):2036-47.

73. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet (London, England). 2014;383(9930):1749-61.

74. Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver international : official journal of the International Association for the Study of the Liver. 2012;32(9):1407-14.

المنارة للاستشارات

ww

75. Ascione A, Fontanella L, Imparato M, Rinaldi L, De Luca M. Mortality from cirrhosis and hepatocellular carcinoma in Western Europe over the last 40 years. Liver international : official journal of the International Association for the Study of the Liver. 2017;37(8):1193-201.

76. Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK. Systematic review: The model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? Alimentary pharmacology & therapeutics. 2005;22(11-12):1079-89.

77. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology (Baltimore, Md). 2001;33(2):464-70.

78. Adam R, Karam V, Cailliez V, JG OG, Mirza D, Cherqui D, et al. 2018 Annual Report of the European Liver Transplant Registry (ELTR) - 50-year evolution of liver transplantation. Transplant international : official journal of the European Society for Organ Transplantation. 2018;31(12):1293-317.

79. EASL Clinical Practice Guidelines: Liver transplantation. Journal of hepatology. 2016;64(2):433-85.

80. Rana A, Ackah RL, Webb GJ, Halazun KJ, Vierling JM, Liu H, et al. No Gains in Long-term Survival After Liver Transplantation Over the Past Three Decades. Annals of surgery. 2019;269(1):20-7.

81. Scandiatransplant figures [Internet]. Scandiatransplant. 2019 (cited 2019-11-18). Available from: http://www.scandiatransplant.org/data/scandiatransplant-figures.

82. Fosby B, Melum E, Bjoro K, Bennet W, Rasmussen A, Andersen IM, et al. Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982-2013. Scandinavian journal of gastroenterology. 2015;50(6):797-808.

83. Tandon P, Raman M, Mourtzakis M, Merli M. A Practical Approach to Nutritional Screening and Assessment in Cirrhosis. Hepatology (Baltimore, Md). 2016.

84. Kerwin AJ, Nussbaum MS. Adjuvant nutrition management of patients with liver failure, including transplant. The Surgical clinics of North America. 2011;91(3):565-78.

85. Quigley EM. Gastrointestinal dysfunction in liver disease and portal hypertension. Gut-liver interactions revisited. Digestive diseases and sciences. 1996;41(3):557-61.

المنارة للاستشارات

86. Kalaitzakis E, Bosaeus I, Ohman L, Bjornsson E. Altered postprandial glucose, insulin, leptin, and ghrelin in liver cirrhosis: correlations with energy intake and resting energy expenditure. The American journal of clinical nutrition. 2007;85(3):808-15.

87. Madden AM, Bradbury W, Morgan MY. Taste perception in cirrhosis: its relationship to circulating micronutrients and food preferences. Hepatology (Baltimore, Md). 1997;26(1):40-8.

88. Dasarathy S. Nutrition and Alcoholic Liver Disease: Effects of Alcoholism on Nutrition, Effects of Nutrition on Alcoholic Liver Disease, and Nutritional Therapies for Alcoholic Liver Disease. Clin Liver Dis. 2016;20(3):535-50.

89. Kim HY, Jang JW. Sarcopenia in the prognosis of cirrhosis: Going beyond the MELD score. World journal of gastroenterology : WJG. 2015;21(25):7637-47.

90. Campos AC, Matias JE, Coelho JC. Nutritional aspects of liver transplantation. Current opinion in clinical nutrition and metabolic care. 2002;5(3):297-307.

91. Tsiaousi ET, Hatzitolios AI, Trygonis SK, Savopoulos CG. Malnutrition in end stage liver disease: recommendations and nutritional support. Journal of gastroenterology and hepatology. 2008;23(4):527-33.

92. Berzigotti A, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Morillas R, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. Hepatology (Baltimore, Md). 2011;54(2):555-61.

93. Gunsar F, Raimondo ML, Jones S, Terreni N, Wong C, Patch D, et al. Nutritional status and prognosis in cirrhotic patients. Alimentary pharmacology & therapeutics. 2006;24(4):563-72.

94. Child CG, Turcotte JG. Surgery and portal hypertension. Major problems in clinical surgery. 1964;1:1-85.

95. Kamath PS, Kim WR, Advanced Liver Disease Study G. The model for end-stage liver disease (MELD). Hepatology (Baltimore, Md). 2007;45(3):797-805.

96. Hamaguchi Y, Kaido T, Okumura S, Kobayashi A, Shirai H, Yagi S, et al. Proposal of Muscle-MELD Score, Including Muscularity, for Prediction of Mortality After Living Donor Liver Transplantation. Transplantation. 2016;100(11):2416-23.

97. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JX, et al. Inclusion of Sarcopenia Within MELD (MELD-Sarcopenia) and the Prediction of Mortality in Patients With Cirrhosis. Clinical and translational gastroenterology. 2015;6:e102.

المنارة للاستشارات

ww

98. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2012;18(10):1209-16.

99. Carvalho L, Parise ER. Evaluation of nutritional status of nonhospitalized patients with liver cirrhosis. Arquivos de gastroenterologia. 2006;43(4):269-74.

100. Ferreira LG, Anastacio LR, Lima AS, Correia MI. Assessment of nutritional status of patients waiting for liver transplantation. Clinical transplantation. 2011;25(2):248-54.

101. Cruz RJ, Jr., Dew MA, Myaskovsky L, Goodpaster B, Fox K, Fontes P, et al. Objective radiologic assessment of body composition in patients with end-stage liver disease: going beyond the BMI. Transplantation. 2013;95(4):617-22.

102. Harimoto N, Yoshizumi T, Izumi T, Motomura T, Harada N, Itoh S, et al. Clinical Outcomes of Living Liver Transplantation According to the Presence of Sarcopenia as Defined by Skeletal Muscle Mass, Hand Grip, and Gait Speed. Transplant Proc. 2017;49(9):2144-52.

103. Montano-Loza AJ, Meza-Junco J, Baracos VE, Prado CM, Ma M, Meeberg G, et al. Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2014;20(6):640-8.

104. Huisman EJ, Trip EJ, Siersema PD, van Hoek B, van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. Eur J Gastroenterol Hepatol. 2011;23(11):982-9.

105. Merli M, Giusto M, Lucidi C, Giannelli V, Pentassuglio I, Di Gregorio V, et al. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. Metabolic brain disease. 2013;28(2):281-4.

106. Maharshi S, Sharma BC, Sachdeva S, Srivastava S, Sharma P. Efficacy of Nutritional Therapy for Patients With Cirrhosis and Minimal Hepatic Encephalopathy in a Randomized Trial. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2016;14(3):454-60 e3; quiz e33.

107. Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C, et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. Journal of clinical gastroenterology. 2013;47(10):861-70.

المنارة للاستشارات

ww

108. Wang CW, Feng S, Covinsky KE, Hayssen H, Zhou LQ, Yeh BM, et al. A Comparison of Muscle Function, Mass, and Quality in Liver Transplant Candidates: Results From the Functional Assessment in Liver Transplantation Study. Transplantation. 2016;100(8):1692-8.

109. Wells CI, McCall JL, Plank LD. Relationship Between Total Body Protein and Cross-Sectional Skeletal Muscle Area in Liver Cirrhosis Is Influenced by Overhydration. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2019;25(1):45-55.

110. DiMartini A, Cruz RJ, Jr., Dew MA, Myaskovsky L, Goodpaster B, Fox K, et al. Muscle mass predicts outcomes following liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2013;19(11):1172-80.

111. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016;59(6):1121-40.

112. Raynard B, Balian A, Fallik D, Capron F, Bedossa P, Chaput JC, et al. Risk factors of fibrosis in alcohol-induced liver disease. Hepatology (Baltimore, Md). 2002;35(3):635-8.

113. Everhart JE, Lok AS, Kim HY, Morgan TR, Lindsay KL, Chung RT, et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Gastroenterology. 2009;137(2):549-57.

114. Berzigotti A, Albillos A, Villanueva C, Genesca J, Ardevol A, Augustin S, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. Hepatology (Baltimore, Md). 2017;65(4):1293-305.

115. Choudhary NS, Saigal S, Saraf N, Mohanka R, Rastogi A, Goja S, et al. Sarcopenic obesity with metabolic syndrome: a newly recognized entity following living donor liver transplantation. Clinical transplantation. 2015;29(3):211-5.

116. Hara N, Iwasa M, Sugimoto R, Mifuji-Moroka R, Yoshikawa K, Terasaka E, et al. Sarcopenia and Sarcopenic Obesity Are Prognostic Factors for Overall Survival in Patients with Cirrhosis. Internal medicine (Tokyo, Japan). 2016;55(8):863-70.

117. Calvert MJ, Freemantle N. Use of health-related quality of life in prescribing research. Part 1: why evaluate health-related quality of life? Journal of Clinical Pharmacy and Therapeutics. 2003;28(6):513-21.

المنارة للاستشارات

ww

118. Gutteling JJ, de Man RA, van der Plas SM, Schalm SW, Busschbach JJ, Darlington AS. Determinants of quality of life in chronic liver patients. Alimentary pharmacology & therapeutics. 2006;23(11):1629-35.

119. Afendy A, Kallman JB, Stepanova M, Younoszai Z, Aquino RD, Bianchi G, et al. Predictors of health-related quality of life in patients with chronic liver disease. Alimentary pharmacology & therapeutics. 2009;30(5):469-76.

120. Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. The American journal of gastroenterology. 2001;96(7):2199-205.

121. Zuberi BF, Memon AR, Afsar S, Qadeer R, Kumar R. Correlation of quality of life in patients of cirrhosis of liver with etiology and disease severity using disease-specific quality of life questionnaire. Journal of Ayub Medical College, Abbottabad : JAMC. 2007;19(2):7-11.

122. Les I, Doval E, Flavia M, Jacas C, Cardenas G, Esteban R, et al. Quality of life in cirrhosis is related to potentially treatable factors. Eur J Gastroenterol Hepatol. 2010;22(2):221-7.

123. Arguedas MR, DeLawrence TG, McGuire BM. Influence of hepatic encephalopathy on health-related quality of life in patients with cirrhosis. Digestive diseases and sciences. 2003;48(8):1622-6.

124. Marchesini G, Bianchi G, Amodio P, Salerno F, Merli M, Panella C, et al. Factors associated with poor health-related quality of life of patients with cirrhosis. Gastroenterology. 2001;120(1):170-8.

125. Bemeur C, Desjardins P, Butterworth RF. Role of nutrition in the management of hepatic encephalopathy in end-stage liver failure. Journal of nutrition and metabolism. 2010;2010:489823.

126. Eghtesad S, Poustchi H, Malekzadeh R. Malnutrition in liver cirrhosis:the influence of protein and sodium. Middle East journal of digestive diseases. 2013;5(2):65-75.

127. Sumskiene J, Kupcinskas L, Sumskas L. Health-related quality of life measurement in chronic liver disease patients. Medicina (Kaunas, Lithuania). 2015;51(4):201-8.

128. Souza NP, Villar LM, Garbin AJ, Rovida TA, Garbin CA. Assessment of health-related quality of life and related factors in patients with chronic liver disease. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases. 2015;19(6):590-5.

المنارة للاستشارات

129. Hauser W, Holtmann G, Grandt D. Determinants of health-related quality of life in patients with chronic liver diseases. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2004;2(2):157-63.

130. Thiele M, Askgaard G, Timm HB, Hamberg O, Gluud LL. Predictors of health-related quality of life in outpatients with cirrhosis: results from a prospective cohort. Hepatitis research and treatment. 2013;2013:479639.

131. Panagaria N, Varma K, Nijhawan S, Rai RR. Nutritional status and quality of life at varying degrees of clinical severity of chronic liver disease. Nutrition & Food Science. 2010;40(6):581-90.

132. Rojas-Loureiro G, Servin-Caamano A, Perez-Reyes E, Servin-Abad L, Higuera-de la Tijera F. Malnutrition negatively impacts the quality of life of patients with cirrhosis: An observational study. World journal of hepatology. 2017;9(5):263-9.

133. Lis CG, Gupta D, Lammersfeld CA, Markman M, Vashi PG. Role of nutritional status in predicting quality of life outcomes in cancer--a systematic review of the epidemiological literature. Nutrition journal. 2012;11:27.

134. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Annals of surgery. 2009;250(2):187-96.

135. Hind K, Oldroyd B, Truscott JG. In vivo precision of the GE Lunar iDXA densitometer for the measurement of total body composition and fat distribution in adults. European journal of clinical nutrition. 2011;65(1):140-2.

136. Kvist H, Chowdhury B, Grangard U, Tylen U, Sjostrom L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. The American journal of clinical nutrition. 1988;48(6):1351-61.

137. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985). 1998;85(1):115-22.

138. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta physiologica (Oxford, England). 2014;210(3):489-97.

139. Rasband W. ImageJ 1.50c. http://imagej.nih.gov/ij: National Institutes of Health, USA.

المنارة للاستشارات

ww

140. Nieman DC, Austin MD, Benezra L, Pearce S, McInnis T, Unick J, et al. Validation of Cosmed's FitMate in measuring oxygen consumption and estimating resting metabolic rate. Research in sports medicine (Print). 2006;14(2):89-96.

141. Lupinsky L, Singer P, Theilla M, Grinev M, Hirsh R, Lev S, et al. Comparison between two metabolic monitors in the measurement of resting energy expenditure and oxygen consumption in diabetic and non-diabetic ambulatory and hospitalized patients. Nutrition (Burbank, Los Angeles County, Calif). 2015;31(1):176-9.

142. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. The Journal of physiology. 1949;109(1-2):1-9.

143. Perseghin G, Mazzaferro V, Benedini S, Pulvirenti A, Coppa J, Regalia E, et al. Resting energy expenditure in diabetic and nondiabetic patients with liver cirrhosis: relation with insulin sensitivity and effect of liver transplantation and immunosuppressive therapy. The American journal of clinical nutrition. 2002;76(3):541-8.

144. Plevak DJ, DiCecco SR, Wiesner RH, Porayko MK, Wahlstrom HE, Janzow DJ, et al. Nutritional support for liver transplantation: identifying caloric and protein requirements. Mayo Clinic proceedings. 1994;69(3):225-30.

145. Nordic Nutrition Recommendations 2012 : Integrating nutrition and physical activity. 5 ed. Copenhagen: Nordic Council of Minister; 2014 2014. 627 p.

146. Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. European journal of clinical nutrition. 1996;50(2):72-92.

147. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut. 1999;45(2):295-300.

148. Benito de Vale M, Josefsson A, Lindkvist B, Kalaitzakis E. Validation of the Swedish version of the chronic liver disease questionnaire. Scandinavian journal of gastroenterology. 2012;47(5):614-5.

149. Borre M, Dam GA, Knudsen AW, Gronbaek H. Nutritional status and nutritional risk in patients with neuroendocrine tumors. Scandinavian journal of gastroenterology. 2018;53(3):284-92.

150. Coin A, Sergi G, Minicuci N, Giannini S, Barbiero E, Manzato E, et al. Fat-free mass and fat mass reference values by dual-energy X-ray absorptiometry (DEXA) in a 20-80 year-old Italian population. Clinical nutrition (Edinburgh, Scotland). 2008;27(1):87-94.

المنارة للاستشارات

151. Coin A, Sarti S, Ruggiero E, Giannini S, Pedrazzoni M, Minisola S, et al. Prevalence of sarcopenia based on different diagnostic criteria using DEXA and appendicular skeletal muscle mass reference values in an Italian population aged 20 to 80. J Am Med Dir Assoc. 2013;14(7):507-12.

152. Gould H, Brennan SL, Kotowicz MA, Nicholson GC, Pasco JA. Total and appendicular lean mass reference ranges for Australian men and women: the Geelong osteoporosis study. Calcified tissue international. 2014;94(4):363-72.

153. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. J Clin Epidemiol. 1996;49(8):907-16.

154. Gillon R. Medical ethics: four principles plus attention to scope. BMJ (Clinical research ed). 1994;309(6948):184-8.

155. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clinical nutrition (Edinburgh, Scotland). 2015;34(3):335-40.

156. Schlussel MM, dos Anjos LA, de Vasconcellos MT, Kac G. Reference values of handgrip dynamometry of healthy adults: a population-based study. Clinical nutrition (Edinburgh, Scotland). 2008;27(4):601-7.

157. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clinical nutrition (Edinburgh, Scotland). 2003;22(4):415-21.

158. To Prevent and Treat Malnutrition, Knowledge based guidelines in Health Care and Social Services: The National Board of Health and Welfare, Sweden; 2019. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2019-5-6.pdf.

159. McCullough AJ, Mullen KD, Kalhan SC. Measurements of total body and extracellular water in cirrhotic patients with and without ascites. Hepatology (Baltimore, Md). 1991;14(6):1102-11.

160. Haderslev KV, Svendsen OL, Staun M. Does paracentesis of ascites influence measurements of bone mineral or body composition by dual-energy x-ray absorptiometry? Metabolism: clinical and experimental. 1999;48(3):373-7.

161. Labio ED, Del Rosario DB, Strasser SI, McCaughan GW, Crawford BA. Effect of ascites on bone density measurement in cirrhosis. J Clin Densitom. 2007;10(4):391-4.

162. Burra P, De Martin E, Gitto S, Villa E. Influence of age and gender before and after liver transplantation. Liver transplantation : official publication of the

المنارة للاستشارات

ww

American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2013;19(2):122-34.

163. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet (London, England). 1997;349(9055):825-32.

164. Sun J, Robinson L, Lee NL, Welles S, Evans AA. No contribution of lifestyle and environmental exposures to gender discrepancy of liver disease severity in chronic hepatitis b infection: Observations from the Haimen City cohort. PloS one. 2017;12(4):e0175482.

165. Sagnelli E, Stroffolini T, Sagnelli C, Pirisi M, Babudieri S, Colloredo G, et al. Gender differences in chronic liver diseases in two cohorts of 2001 and 2014 in Italy. Infection. 2018;46(1):93-101.

166. Westerling R. Decreasing gender differences in "avoidable" mortality in Sweden. Scandinavian journal of public health. 2003;31(5):342-9.

167. Equal care? Gender perspective on Health Care: The National Board of Health and Welfare, Sweden; 2004. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/ovrigt/2004-103-3_20041033.pdf.

168. Peng S, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. The American journal of clinical nutrition. 2007;85(5):1257-66.

169. Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial. Journal of hepatology. 2016;65(5):906-13.

170. Zambrano DN, Xiao J, Prado CM, Gonzalez MC. Patient-Generated Subjective Global Assessment and Computed Tomography in the assessment of malnutrition and sarcopenia in patients with cirrhosis: Is there any association? Clinical nutrition (Edinburgh, Scotland). 2019.

171. Kalafateli M, Mantzoukis K, Choi Yau Y, Mohammad AO, Arora S, Rodrigues S, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. Journal of cachexia, sarcopenia and muscle. 2017;8(1):113-21.

172. Aberg F, Gissler M, Karlsen TH, Ericzon BG, Foss A, Rasmussen A, et al. Differences in long-term survival among liver transplant recipients and the general population: a population-based Nordic study. Hepatology (Baltimore, Md). 2015;61(2):668-77.

المنارة للاستشارات

173. Toledo AH, Carroll T, Arnold E, Tulu Z, Caffey T, Kearns LE, et al. Reducing liver transplant length of stay: a Lean Six Sigma approach. Progress in transplantation (Aliso Viejo, Calif). 2013;23(4):350-64.

174. Ney M, Gramlich L, Mathiesen V, Bailey RJ, Haykowsky M, Ma M, et al. Patient-perceived barriers to lifestyle interventions in cirrhosis. Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association. 2017;23(2):97-104.

175. Fritz E, Hammer J. Gastrointestinal symptoms in patients with liver cirrhosis are linked to impaired quality of life and psychological distress. Eur J Gastroenterol Hepatol. 2009;21(4):460-5.

176. Chiu E, Marr K, Taylor L, Lam L, Stapleton M, Tandon P, et al. Malnutrition Impacts Health-Related Quality of Life in Cirrhosis: A Cross-Sectional Study. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2020;35(1):119-25.

177. Yamanaka-Okumura H, Nakamura T, Miyake H, Takeuchi H, Katayama T, Morine Y, et al. Effect of long-term late-evening snack on health-related quality of life in cirrhotic patients. Hepatology research : the official journal of the Japan Society of Hepatology. 2010;40(5):470-6.

178. Bardel A, Wallander MA, Wallman T, Rosengren A, Johansson S, Eriksson H, et al. Age and sex related self-reported symptoms in a general population across 30 years: Patterns of reporting and secular trend. PloS one. 2019;14(2):e0211532.

179. Blom V, Kallings LV, Ekblom B, Wallin P, Andersson G, Hemmingsson E, et al. Self-Reported General Health, Overall and Work-Related Stress, Loneliness, and Sleeping Problems in 335,625 Swedish Adults from 2000 to 2016. International journal of environmental research and public health. 2020;17(2).

180. Marberg T, Karling P, Soderberg K, Anan I, Wixner J. Self-reported gastrointestinal symptoms are more common in liver transplanted transthyretin amyloidosis patients than in healthy controls and in patients transplanted for end-stage liver disease. Amyloid : the international journal of experimental and clinical investigation : the official journal of the International Society of Amyloidosis. 2019;26(sup1):47-8.

181. Lindqvist C, Slinde F, Majeed A, Bottai M, Wahlin S. Nutrition impact symptoms are related to malnutrition and quality of life - A cross-sectional study of patients with chronic liver disease. Clinical nutrition (Edinburgh, Scotland). 2019.

المنارة للاستشارات

ww

182. Hasse JM, Blue LS, Liepa GU, Goldstein RM, Jennings LW, Mor E, et al. Early enteral nutrition support in patients undergoing liver transplantation. JPEN Journal of parenteral and enteral nutrition. 1995;19(6):437-43.

183. Ribeiro HS, Coury NC, Generoso SD, Lima AS, Correia MITD. Energy Balance and Nutrition Status: A Prospective Assessment of Patients Undergoing Liver Transplantation. Nutrition in Clinical Practice. 2020;35(1):126-32.

184. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clinical nutrition (Edinburgh, Scotland). 2019;38(1):48-79.

185. Kyoung KH, Lee SG, Nam CW, Nah YW. Beneficial effect of low caloric intake in the early period after orthotopic liver transplantation: a new concept using graft weight. Hepato-gastroenterology. 2014;61(134):1668-72.

186. Sugihara K, Yamanaka-Okumura H, Teramoto A, Urano E, Katayama T, Morine Y, et al. Recovery of nutritional metabolism after liver transplantation. Nutrition (Burbank, Los Angeles County, Calif). 2015;31(1):105-10.

187. Ferreira LG, Santos LF, Anastacio LR, Lima AS, Correia MI. Resting energy expenditure, body composition, and dietary intake: a longitudinal study before and after liver transplantation. Transplantation. 2013;96(6):579-85.

188. Muller MJ, Loyal S, Schwarze M, Lobers J, Selberg O, Ringe B, et al. Resting energy expenditure and nutritional state in patients with liver cirrhosis before and after liver transplantation. Clinical nutrition (Edinburgh, Scotland). 1994;13(3):145-52.

189. Plank LD, Metzger DJ, McCall JL, Barclay KL, Gane EJ, Streat SJ, et al. Sequential changes in the metabolic response to orthotopic liver transplantation during the first year after surgery. Annals of surgery. 2001;234(2):245-55.

190. Eslamparast T, Vandermeer B, Raman M, Gramlich L, Den Heyer V, Belland D, et al. Are Predictive Energy Expenditure Equations Accurate in Cirrhosis? Nutrients. 2019;11(2):334.

191. Kruizenga HM, Hofsteenge GH, Weijs PJ. Predicting resting energy expenditure in underweight, normal weight, overweight, and obese adult hospital patients. Nutrition & metabolism. 2016;13:85.

192. Madden AM, Morgan MY. Resting energy expenditure should be measured in patients with cirrhosis, not predicted. Hepatology (Baltimore, Md). 1999;30(3):655-64.

المنارة للاستشارات

193. Frankenfield DC, Ashcraft CM. Toward the Development of Predictive Equations for Resting Metabolic Rate in Acutely Ill Spontaneously Breathing Patients. JPEN Journal of parenteral and enteral nutrition. 2017;41(7):1155-61.

194. Siervo M, Bertoli S, Battezzati A, Wells JC, Lara J, Ferraris C, et al. Accuracy of predictive equations for the measurement of resting energy expenditure in older subjects. Clinical nutrition (Edinburgh, Scotland). 2014;33(4):613-9.

195. Taflin H, Hafstrom L, Holmberg E, Castedal M, Lindner P. The impact of increased immigration to Sweden on the incidence and treatment of patients with HCC and underlying liver disease. Scandinavian journal of gastroenterology. 2019;54(6):746-52.

196. Rothman K. Epidemiology- An Introduction. 2nd edition ed: Oxford University Press; 2012.

197. Morsbach F, Zhang YH, Martin L, Lindqvist C, Brismar T. Body composition evaluation with computed tomography: Contrast media and slice thickness cause methodological errors. Nutrition (Burbank, Los Angeles County, Calif). 2019;59:50-5.

198. Boutin RD, Kaptuch JM, Bateni CP, Chalfant JS, Yao L. Influence of IV Contrast Administration on CT Measures of Muscle and Bone Attenuation: Implications for Sarcopenia and Osteoporosis Evaluation. AJR American journal of roentgenology. 2016;207(5):1046-54.

199. Morsbach F, Zhang YH, Nowik P, Martin L, Lindqvist C, Svensson A, et al. Influence of tube potential on CT body composition analysis. Nutrition (Burbank, Los Angeles County, Calif). 2018;53:9-13.

200. van Vugt JL, Levolger S, Gharbharan A, Koek M, Niessen WJ, Burger JW, et al. A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. Journal of cachexia, sarcopenia and muscle. 2017;8(2):285-97.

201. Feder SL. Data Quality in Electronic Health Records Research: Quality Domains and Assessment Methods. West J Nurs Res. 2018;40(5):753-66.

المنارة للاستشارات

ww

المنارة للاستشارات

ProQuest Number: 28420922

All rights reserved

INFORMATION TO ALL USERS
The quality of this reproduction is dependent on the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript
and there are missing pages, these will be noted. Also, if material had to be removed,
a note will indicate the deletion.

ProQuest 28420922

Published by ProQuest LLC (2021). Copyright of the Dissertation is held by the Author.

All Rights Reserved.
This work is protected against unauthorized copying under Title 17, United States Code
Microform Edition © ProQuest LLC.

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

www.manaraa.com