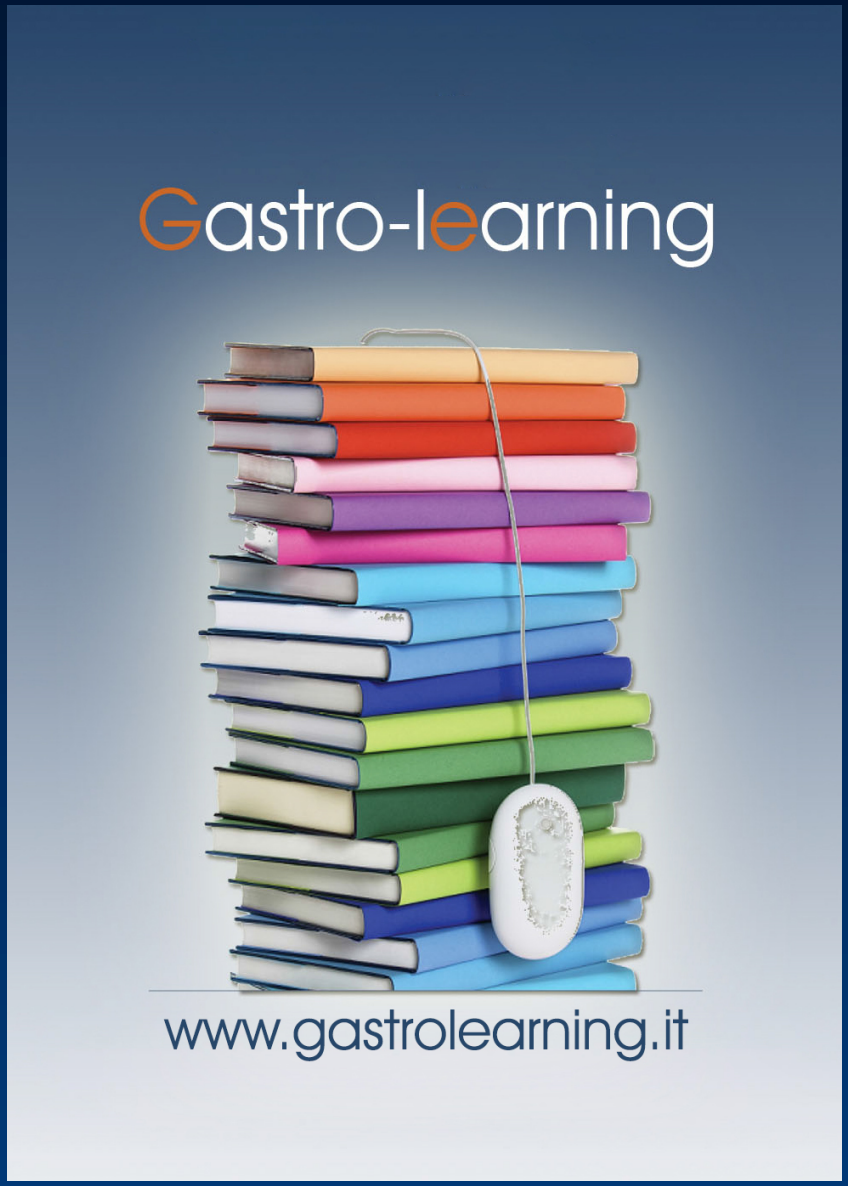
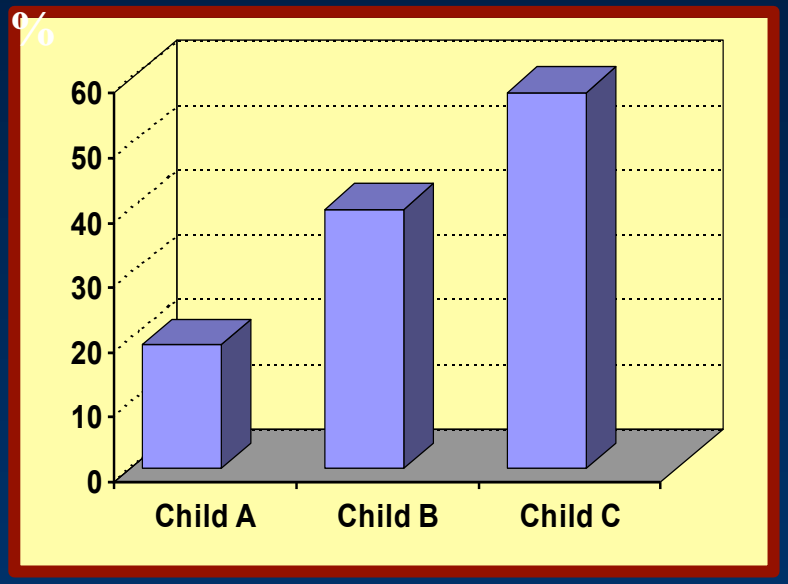
WWW.GASTROLEARNING.IT



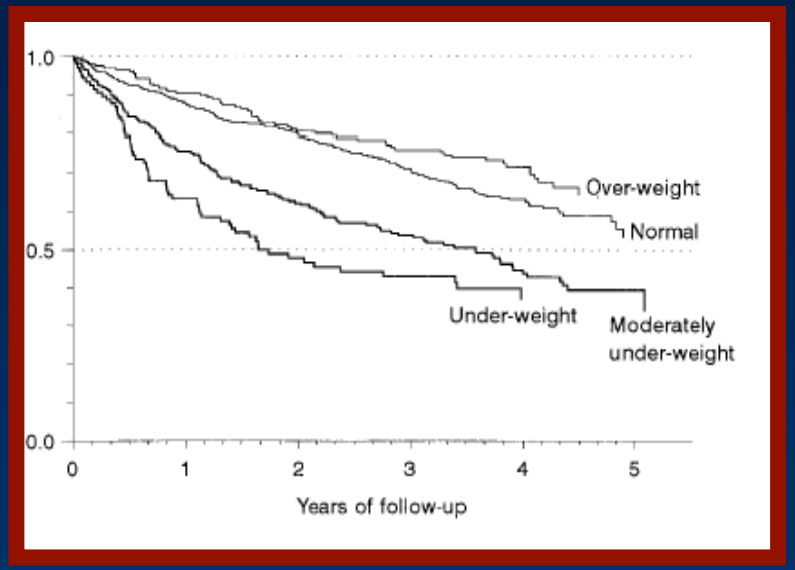
LE NUOVE LINEE GUIDA EASL SULLA NUTRIZIONE NEL PAZIENTE CON EPATOPATIA CRONICA

Manuela Merli
Sapienza Universita' di Roma

Prevalence of malnutrition according to anthropometry in 1402 cirrhotic patients (Policentrica Italiana Nutrizione Cirrosi)

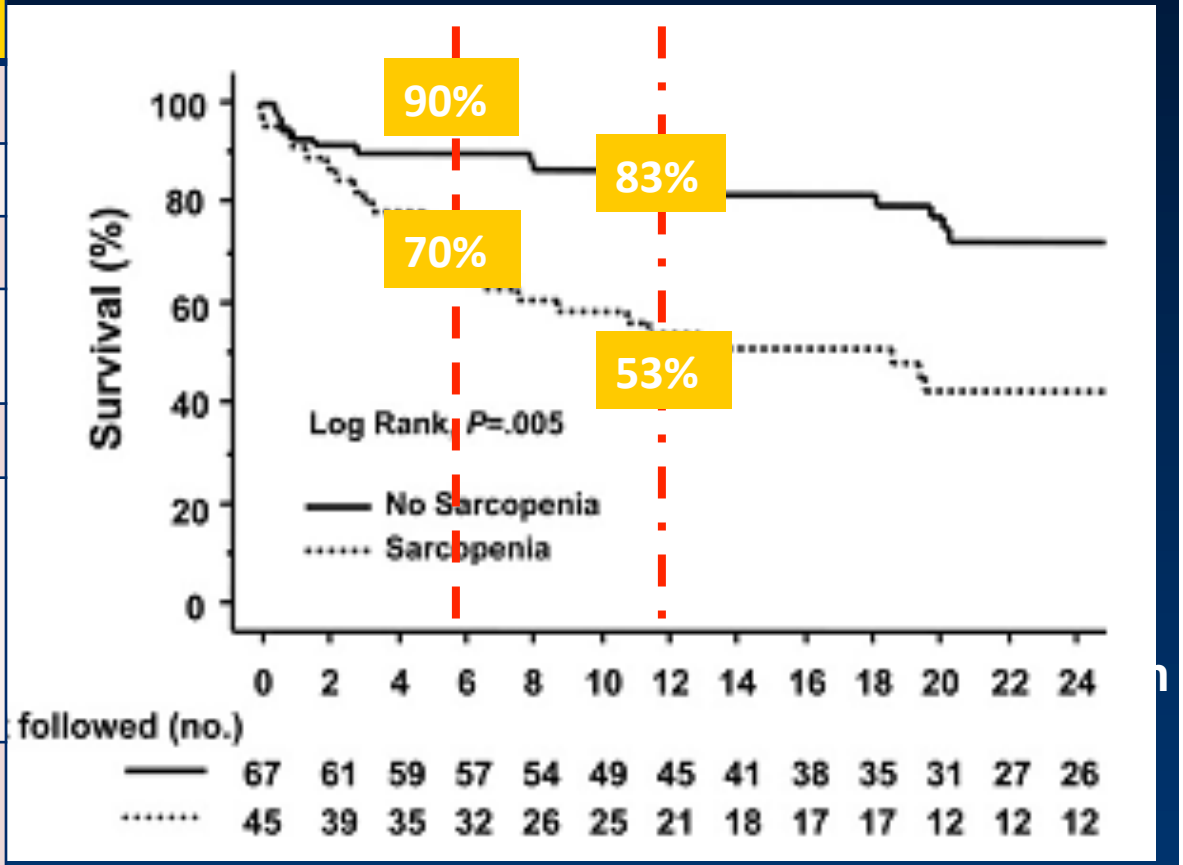


Differences in 5 years survival rates in 1053 cirrhotic patients according to anthropometry (Policentrica Italiana Nutrizione Cirrosi)



Merli M et al Hepatology

Features	N° 112
Age (y)	54±1 (27-71)
Male	78%
BMI>30	27%
CHILD Class A/B/C (%)	11/59/30
MELD	13 (6-36)
Cirrhosis etiology (%) • Alcohol • HCV • Alcohol+HCV • Others	 22 29 16 34
Sarcopenia *(%) •Men •Women •ALL	 50 18 40



(*TC Evaluation)

Montano-Loza 2010

EASL Clinical Practice Guidelines on nutrition in chronic liver disease.

- **Chair**
  - Manuela Merli
- **Panel members**
  - Shira Zelber-Sagi, Srinivasan Dasarathy, Sara Montagnese, Laurence Genton, Mathias Plauth, Albert Parés, Annalisa Berzigotti (EASL Governing Board Representative)
- **Reviewers**
  - Dominique Valla, Stephan Bischoff, Puneeta Tandon

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Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on nutrition in chronic liver disease☆

European Association for the Study of the Liver*

Summary

A frequent complication in liver cirrhosis is malnutrition, which is associated with the progression of liver failure, and with a higher rate of complications including infections, hepatic encephalopathy and ascites. In recent years, the rising prevalence of obesity has led to an increase in the number of cirrhosis cases related to non-alcoholic steatohepatitis. Malnutrition, obesity and sarcopenic obesity may worsen the prognosis of patients with liver cirrhosis and lower their survival. Nutritional monitoring and intervention is therefore crucial in chronic liver disease. These Clinical Practice Guidelines review the present knowledge in the field of nutrition in chronic liver disease and promote further research on this topic. Screening, assessment and principles of nutritional management are examined, with recommendations provided in specific settings such as hepatic encephalopathy, cirrhotic patients with bone disease, patients undergoing liver surgery or transplantation and critically ill cirrhotic patients.

Introduction

Malnutrition is frequently a burden in patients with liver cirrhosis, occurring in 20–50% of patients. The progression of malnutrition is associated with that of liver failure. While malnutrition may be less evident in patients with compensated cirrhosis it is easily recognisable in those with decompensated cirrhosis. Malnutrition has been reported in 20% of patients with compensated cirrhosis and in more than 50% of patients with decompensated liver disease.[1] Both adipose tissue and muscle tissue can be depleted; female patients more frequently develop a depletion in fat deposits while males more rapidly lose muscle tissue.[2,3]

As detailed in these clinical practice guidelines (CPGs), malnutrition and muscle mass loss (sarcopenia), which has often been used as an equivalent of severe malnutrition,[3] are associated with a higher rate of complications[4] such as susceptibility to infections,[5] hepatic encephalopathy (HE)[6] and ascites, [4] as well as being independent predictors of lower survival in cirrhosis[7,8] and in patients undergoing liver transplantation.[9] Given these observations, malnutrition and sarcopenia should be recognised as complications of cirrhosis, which in turn worsen the prognosis of cirrhotic patients.

Whether malnutrition can be reversed in cirrhotic patients is controversial. Although there is general agreement about the need to improve the dietary intake of these patients, by avoiding limitations and restrictions that are not evidence based, amelioration of the nutritional status and muscle mass is not always achievable.[10–12]

Although the term "malnutrition" refers both to deficiencies and to excesses in nutritional status, in the present CPGs "malnutrition" refers to "undernutrition". More recently, in addition to undernutrition, overweight or obesity are increasingly observed in cirrhotic patients because of the increasing number of cirrhosis cases related to non-alcoholic steatohepatitis (NASH). Muscle mass depletion may also occur in these patients, but due to the coexistence of obesity, sarcopenia might be overlooked. Obesity and sarcopenic obesity may worsen the prognosis of patients with liver cirrhosis.[13–15,3]

No previous guidelines released by the European Association for the Study of Liver Disease (EASL) have dealt with nutrition in advanced liver disease and/or have evaluated the relationship between nutritional status and the clinical outcome of patients. Therefore, the EASL Governing Board has asked a panel of experts in the field of nutrition and hepatology to produce the present CPGs.

Methodology

The panel initially established the most relevant questions to answer, considering relevance, urgency and completeness of the topics to be covered. The main questions addressed were: How can nutritional problems be recognised? In which conditions are nutritional assessments recommended? What are the available methods of evaluation? What are the consequences of malnutrition and its correction? Different clinical scenarios have been considered with special attention paid to nutrition in HE and before and after liver transplantation. A section devoted to bone metabolism in chronic liver disease has also been included. Each expert took responsibility and made proposals for statements for a specific section of the guideline.

The literature search was performed in different databases (PubMed, Embase, Google Scholar, Scopus) and a list of pertinent articles was derived from this "first line" search The initial key words were: "Nutrition" OR "Nutritional status" OR "Malnutrition" OR "Sarcopenia" AND "Liver cirrhosis" OR "Chronic liver Disease". Further, more specific key words were also utilised: "nutritional assessment", "nutrition risk", "hepatic

* **Clinical Practice Guideline Panel:** Chair: Manuela Merli, EASL Governing Board representative: Annalisa Berzigotti, Panel members: Shira Zelber-Sagi, Srinivasan Dasarathy, Sara Montagnese, Laurence Genton, Mathias Plauth, Albert Parés.

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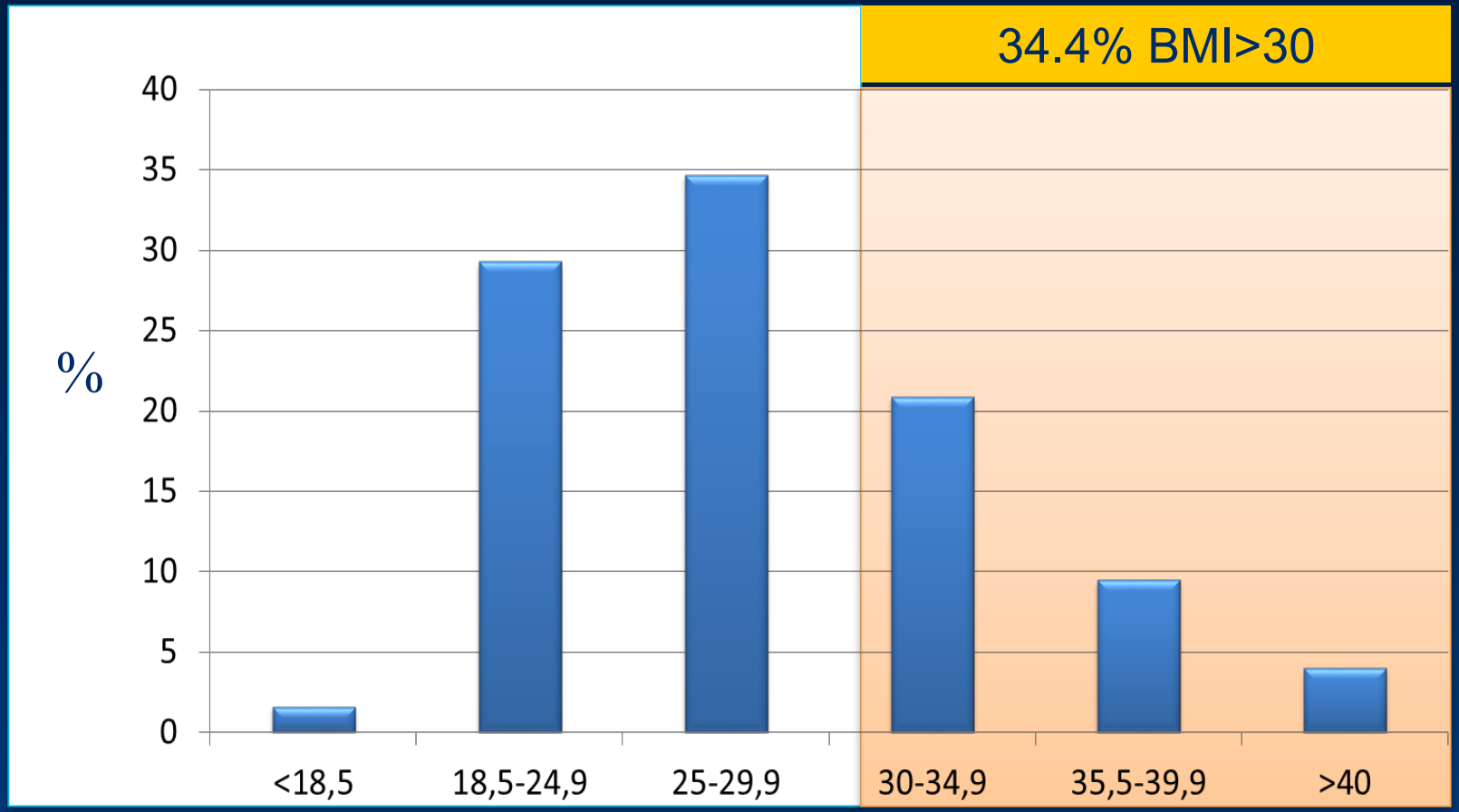
Malnutrition and Chronic liver disease: key points

- "Malnutrition" used as a synonym of "under nutrition"
- More evident in decompensated cirrhosis but may go unrecognized
- Sarcopenia (impairment of muscle mass and function) and frailty
- Both muscle and fat depletion with gender difference

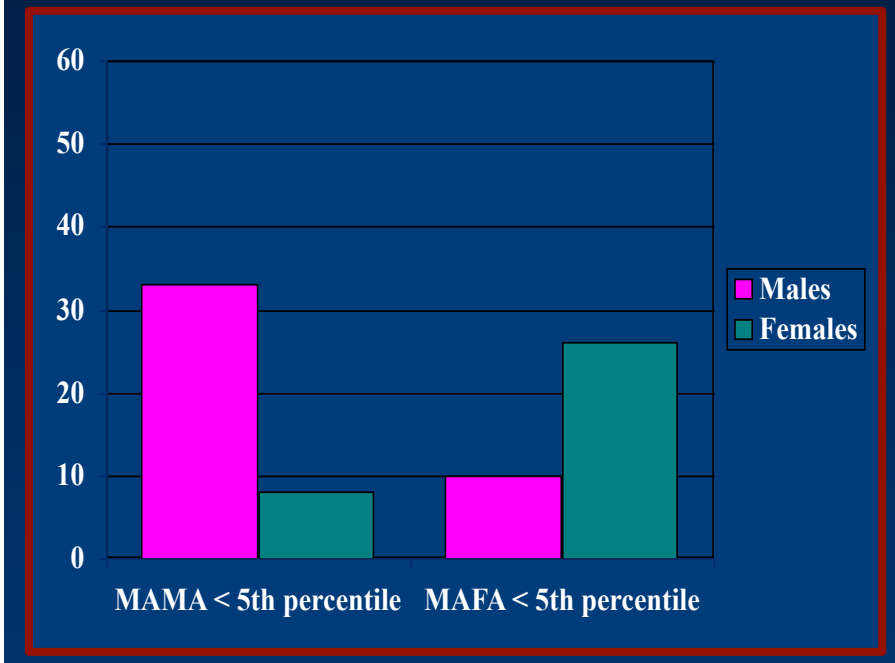
- Overweight or obese patients with cirrhosis increasingly being seen (increased number of cirrhosis related to NASH)
- Sarcopenia also present in obesity (sarcopenic obesity)

Characteristics of 5,805 adult liver transplant recipients in US in 2011 (OPTN & SRTR annual report)



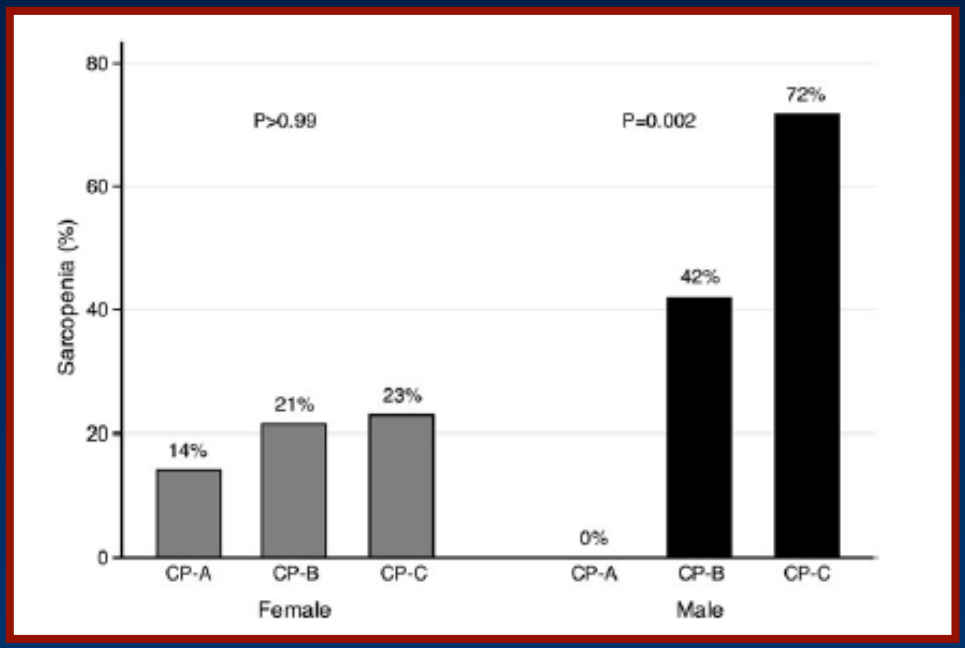
Kim et al Am J Transplant. 20

Gender difference in malnutrition in chronic liver disease



MAMA mid arm muscle area
MAFA mid arm fat area

Merli M, et al. J. Hepatol. 1994



Sarcopenia : TC Assessment

Puneeta Tandon et al, Liver Transplantation 2012

Prevalence and implications of malnutrition and sarcopenia in cirrhosis

- **Malnutrition and sarcopenia [1] favour disease complications:[2]**
  - Susceptibility to infections
  - Hepatic encephalopathy
  - Ascites

- **Malnutrition and sarcopenia worsen the prognosis of the cirrhotic patients**
  - lower survival in cirrhosis
  - lower survival in patients awaiting liver transplantation

  - **Can we reverse malnutrition?**

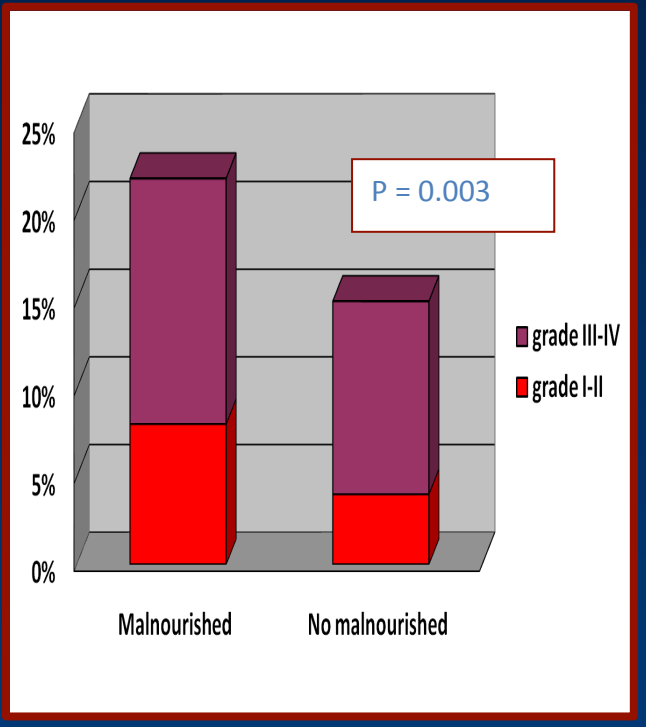
1. Dasarathy S, et al. J Cachexia Sarcopenia Muscle 2012;3:225–37;
2. Huisman EJ, et al. Eur J Gastroenterol Hepatol 2011;23:982–9
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Table 4. Variables Independently Associated With Infection and Sepsis at Multivariate Analysis

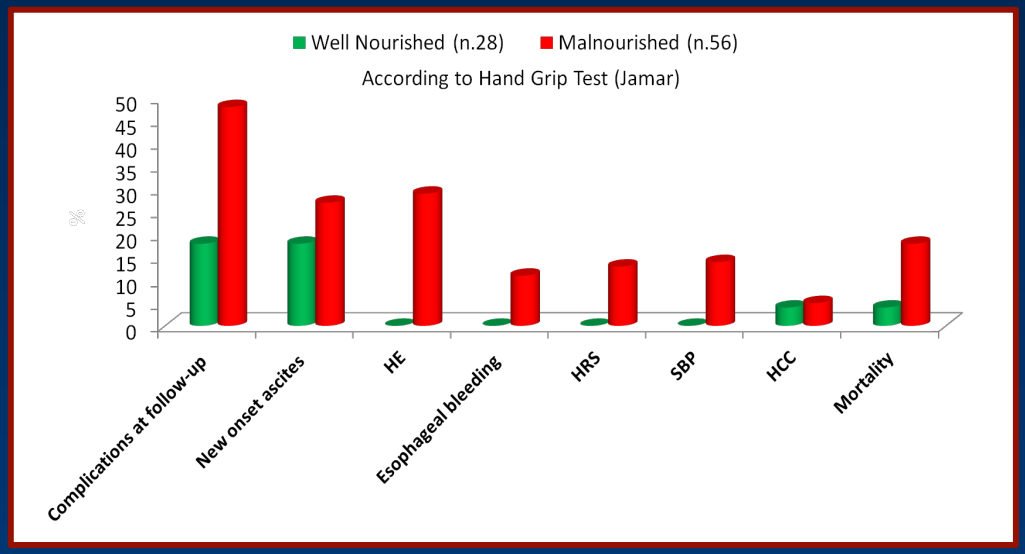
	Infections	Sepsis
Previous infections (past 12 months)	OR, 4.7 95% CI, 2.2–10.6 *P* = .000	OR, 3.4 95% CI, 1.3–8.1 *P* = .007
MELD score, ≥15	OR, 2.8 95% CI, 1.3–6.1 *P* = .001	OR, 4.4 95% CI, 1.8–10 *P* = .001
Protein malnutrition	OR, 4 95% CI, 1.5–10 *P* = .004	OR, 4 95% CI, 1.5–10 *P* = .004

Merli M CGH 2010

	In hospital mortality	Mortality at 6 months follow up
Child C	p= 0,006 O.R.= 6,3;95% CI:1,67-23,7	p= 0,001 O.R.= 4,1 95% CI:1,7-9,7
Sepsis	p=0.0056 O.R=6,01; 95% CI:1,7-21,46	p=0.003 O.R=2,8; 95% CI:1,1- 7,3
Protein Malnutrition	p= 0,0004 O.R.= 10,44 95% CI:2,8-38,5	p= 0,0001; O.R.= 5,6 95% CI:2,3-13,9

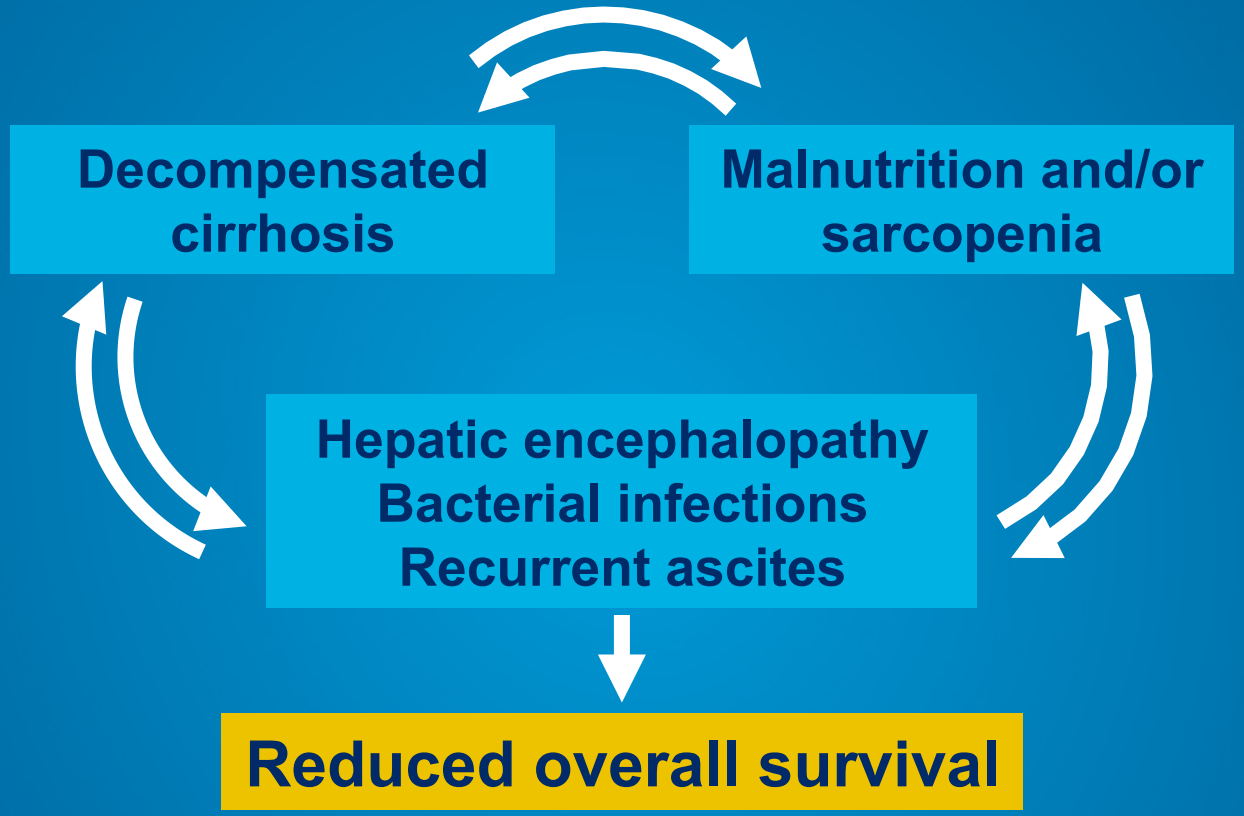


Merli M Metab Brain Dis 2012



Huisman EJ et al; EJGH 2011

Relationship between malnutrition, complications of cirrhosis, transplantation, and survival



- In HCC: increased complications and reduced survival
- After surgery: reduced survival
- In liver transplantation: Increased waiting list mortality and post-operative complications

Tandon P, et al. Hepatology 2017;65:1044–5
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Guideline Topics

1. Screening and assessment for malnutrition and obesity in cirrhosis
2. Nutritional management principles in patients with cirrhosis
3. Approach to sarcopenia in patients with cirrhosis
4. Approach and management of obesity in patients with cirrhosis
5. Micronutrients
6. Nutritional treatment options for hepatic encephalopathy
7. Nutritional treatment options in patients with cirrhosis and bone disease
8. Clinical scenarios requiring special considerations
9. The future for nutrition in chronic liver disease

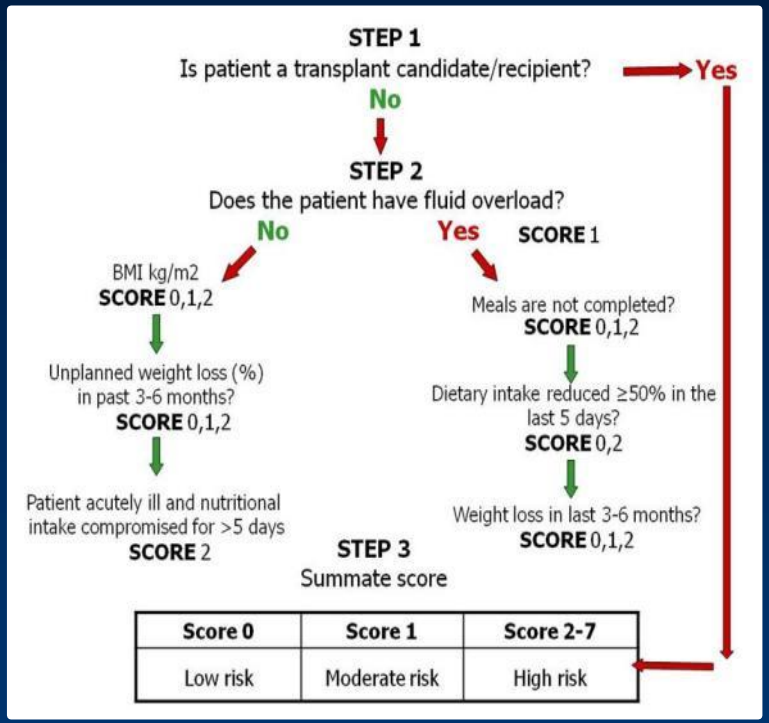
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Screening for malnutrition in cirrhosis

- All patients with advanced chronic liver disease, especially decompensated cirrhosis, should undergo a rapid nutritional screen
- Two criteria stratify patients at high risk of malnutrition:
  - Being underweight (BMI <18.5 kg/m^2)
  - Advanced decompensated cirrhosis (Child–Pugh C)

Recommendations	Grade of evidence	Grade of recommendation
Perform a rapid nutritional screen in all patients with cirrhosis and complete a detailed assessment in those at risk of malnutrition to confirm the presence and severity of malnutrition	II-2 B	1
Assume malnutrition risk is high if BMI <18.5 kg/m^2 or Child–Pugh C. In all other cases, utilize nutritional screening tools to assess risk of malnutrition	II-2 B	1

RFH-Nutrition Prioritizing Tool



LD- Undernutrition Screening Tool

Patients questions are scored to identify malnutrition risk

1. How have you been eating lately?
2. Have you lost any weight in the last year?
3. Have you noticed any loss of fat or thinning of your arm and ribs?
4. Have you noticed any muscle loss in temples legs clavicle or shoulders?
5. Do you have any fluid or swelling in your abdomen or legs?
6. Are you able to participate in your usual activities?

Detailed nutritional assessment: who, when,how

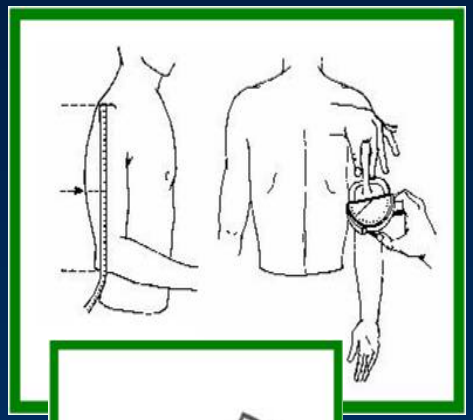
- All patients at risk of malnutrition should undergo detailed nutritional assessment by a registered dietician or nutrition expert
- In patients at high risk of malnutrition, assess each component every 1–6 months in the outpatient setting and for inpatients, at admission and periodically throughout the hospital stay:[1]

*Including mid-arm muscle circumference (MAMC), mid-arm muscular area (MAMA) and triceps skinfold (TSF)

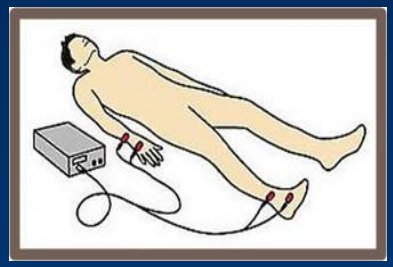
1. Tandon P, et al. Hepatology 2017;65:1044–57; 2. Morgan MY, et al. Hepatology 2006;44:823–35
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Methods for nutritional assessment

ANTHROPOMETRY



DEXA

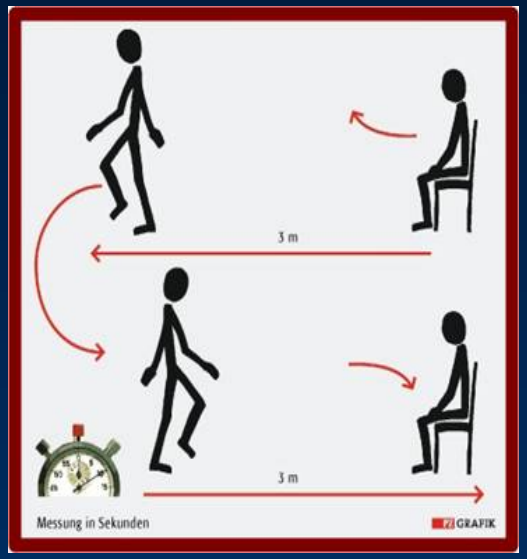


BIA

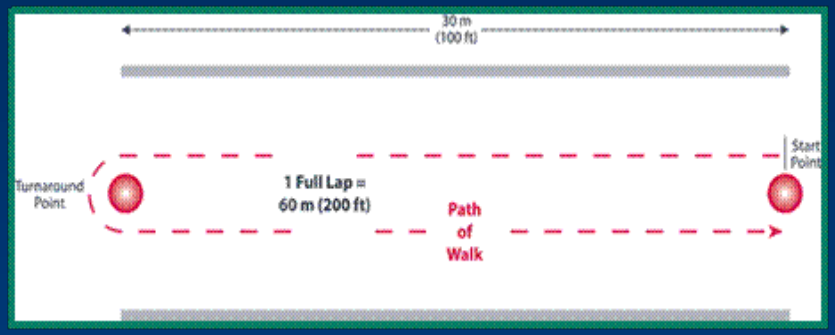
CT SCAN OR RM

Methods for function assessment

HANDGRIP DYNAMOMETER



TEST UP AND GO



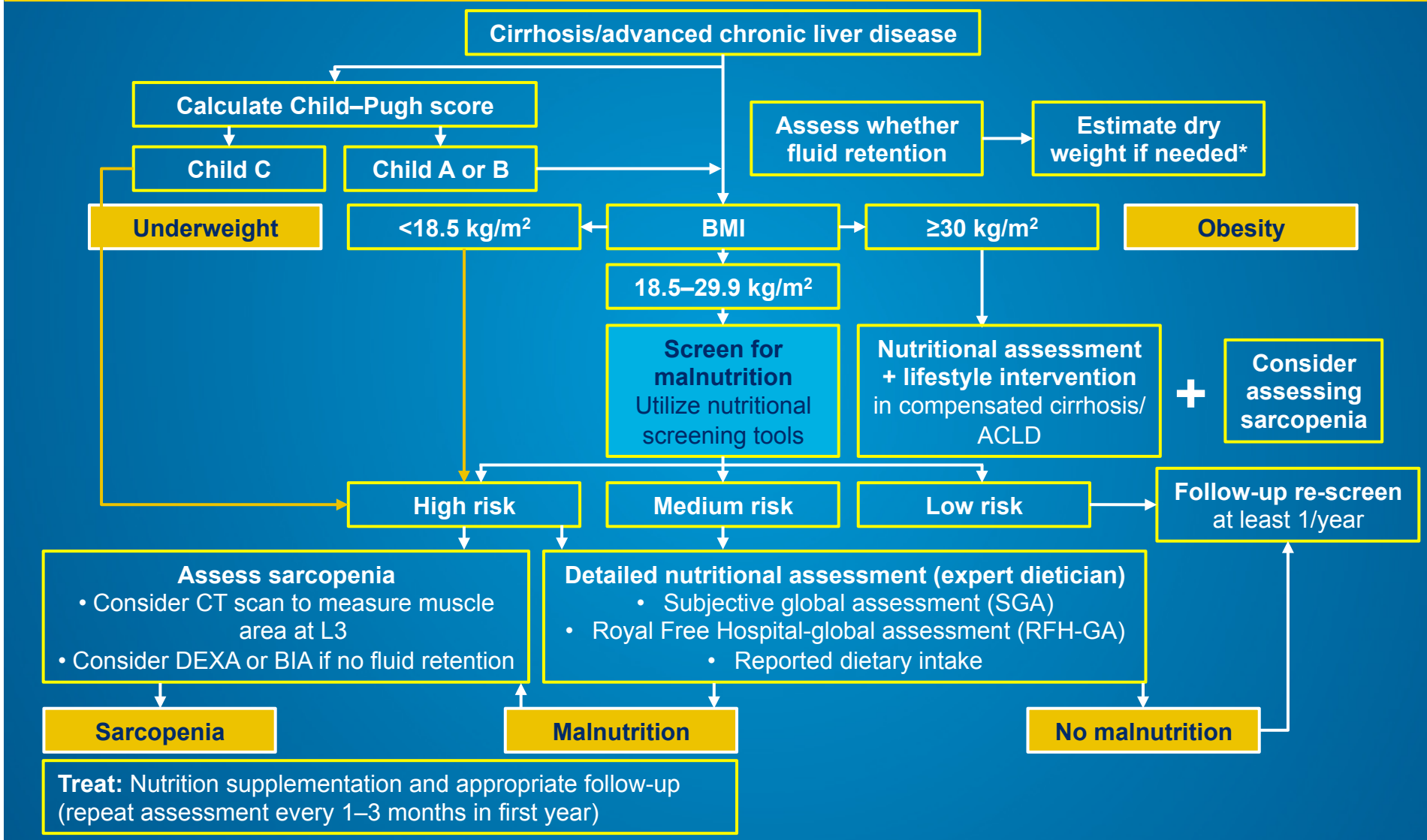
WALK TEST

Detailed nutritional assessment

Recommendations	Grade of evidence	Grade of recommendation
Include an assessment of sarcopenia within the nutritional assessment	II-2 B	1
Assess muscle mass by CT imaging where available (having been performed for other purposes). Anthropometry, DEXA or BIA are possible alternatives, which also allow serial measurements	II-2 B	1
Assess muscle function in the clinical setting with the most appropriate tools, such as handgrip strength (HGS) and/or the short physical performance battery (SPPB)	II-2 B	1
Assessment of dietary intake by trained personnel (ideally a dietician with knowledge of managing patients with liver disease) working as part of a team with the hepatologist. Assessment should include: quality and quantity of food and supplements, fluids, sodium in diet, number and timing of meals during the day and barriers to eating	II-2 B	1

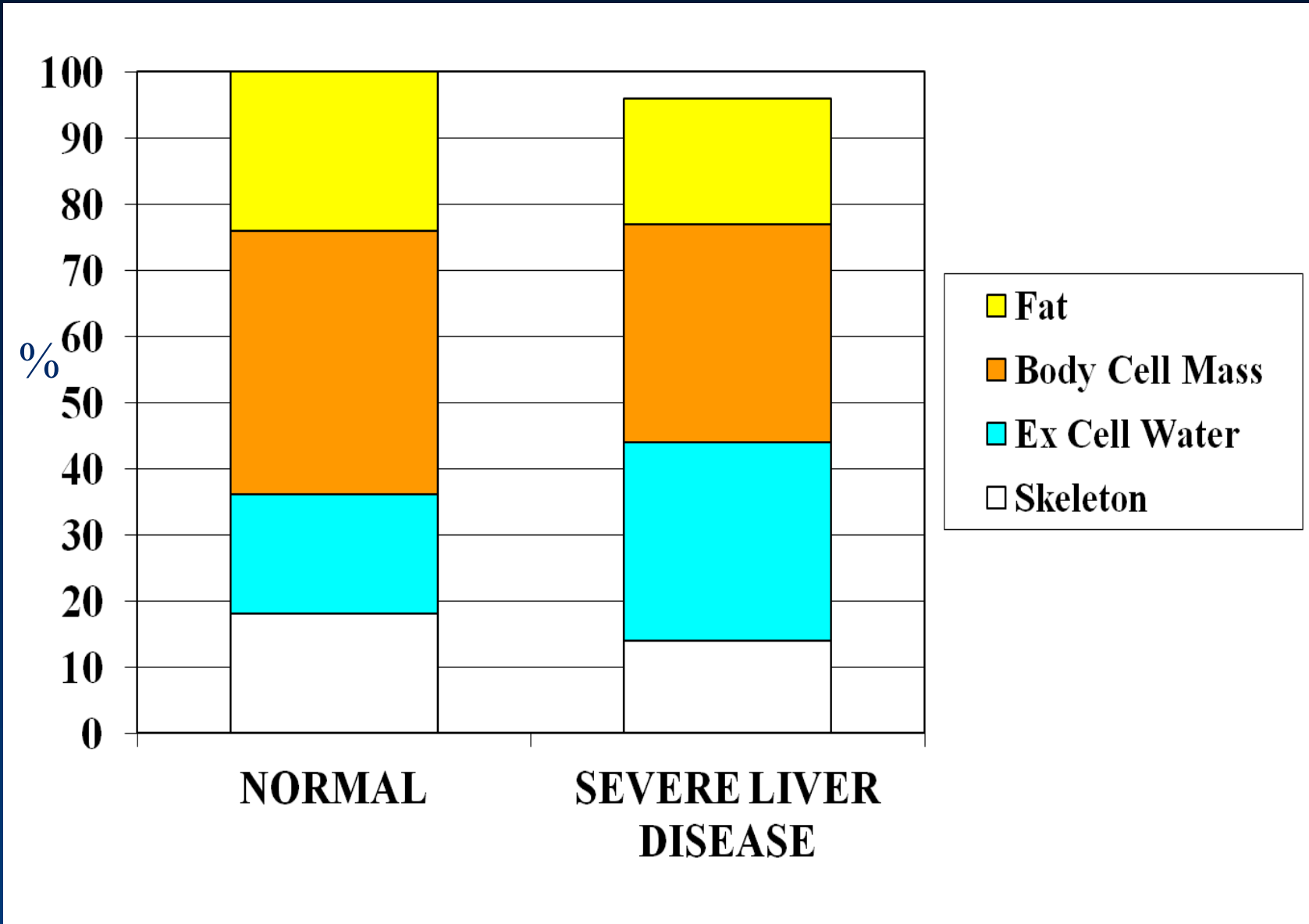
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Nutritional screening and assessment in patients with cirrhosis: Summary



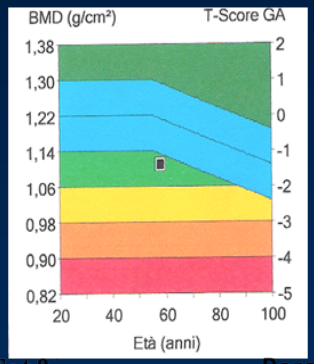
*In the case of fluid retention, body weight should be corrected by evaluating the patient's dry weight by post-paracentesis body weight or weight recorded before fluid retention if available, or by subtracting a percentage of weight based upon severity of ascites (mild, 5%; moderate, 10%; severe, 15%), with an additional 5% subtracted if bilateral pedal oedema is present. EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

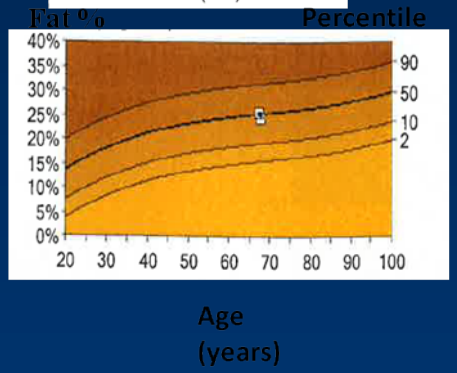
Changes in body composition



Changes in body composition

DEXA

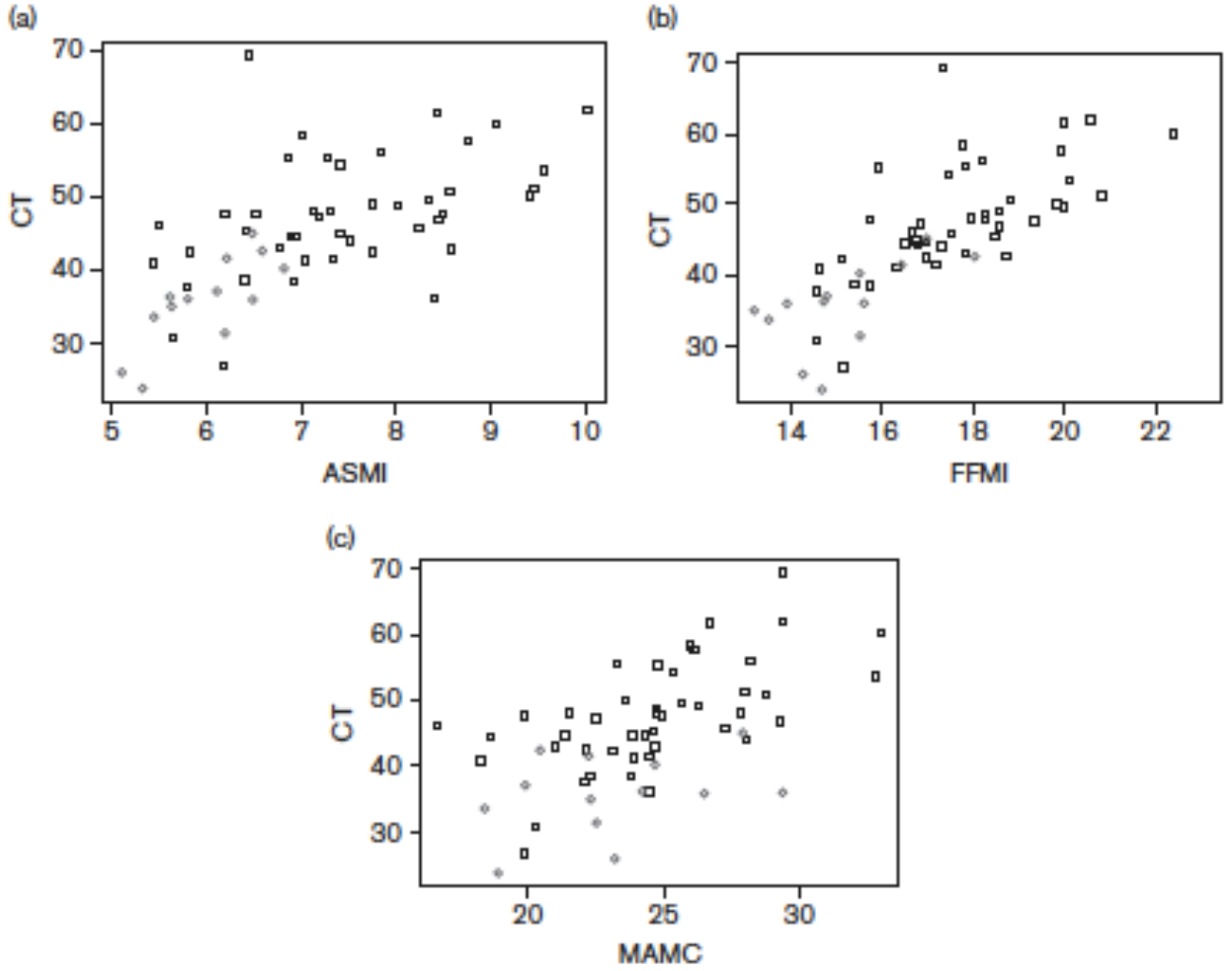




FAT FREE MASS and APPENDICULAR SKELETAL MUSCLE INDEX (ASMI)

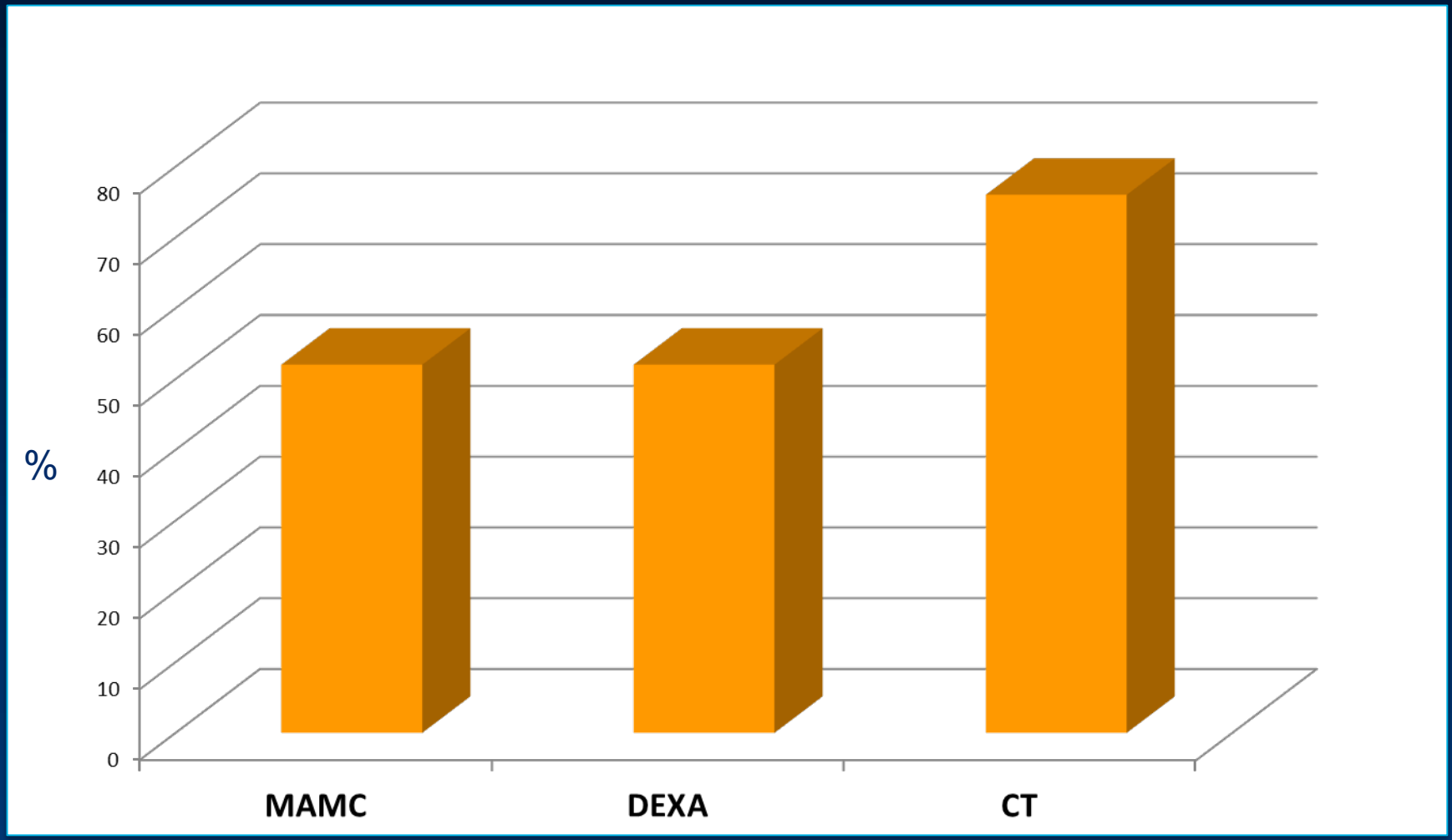
SKELETAL MUSCLE INDEX (SMI)

Agreement among measurements



Scatterplot of the Appendicular Skeletal Muscle Index (ASMI) evaluated by dual-energy X-ray absorptiometry (DEXA) (kg/m^2) (a), Fat-Free Mass Index (FFMI) evaluated by DEXA (kg/m^2) (b), and mid-arm muscle circumference (MAMC) evaluated by anthropometry (cm^2) (c) versus computed tomography (CT) measurement of Skeletal Muscle Index [muscle area (cm^2)/height (m^2)]. Women are represented as circles, whereas men are represented as squares.

Giusto M Eur J Gastroenterol Hepatol. 2015



* DEXA= fat free mass index; CT= skeletal muscle index

Giusto M Eur J Gastroenterol Hepatol. 2015

Nutritional management principles in cirrhosis: Energy and protein requirements

- Cirrhosis is a state of accelerated starvation characterized by a rapid post-absorptive physiology and reduced respiratory quotient
- Energy supply needs to balance total energy expenditure (TEE)

Recommendations	Grade of evidence	Grade of recommendation
Performance of nutritional counselling in patients with malnutrition and cirrhosis by a multidisciplinary team to help the patient achieve adequate calorie and protein intake	II-2 C	2
Optimal daily energy intake should not be lower than the recommended 35 kcal/kg actual BW/day (in non-obese individuals)	II-2 B	1
Optimal daily protein intake should not be lower than the recommended 1.2–1.5 g/kg actual body weight/day	II-2 B	1
Include late evening oral nutritional supplementation (ONS) and breakfast in the dietary regimen of malnourished patients with decompensated cirrhosis	II-1 B	1

*Use of actual BW corrected for ascites is considered safe

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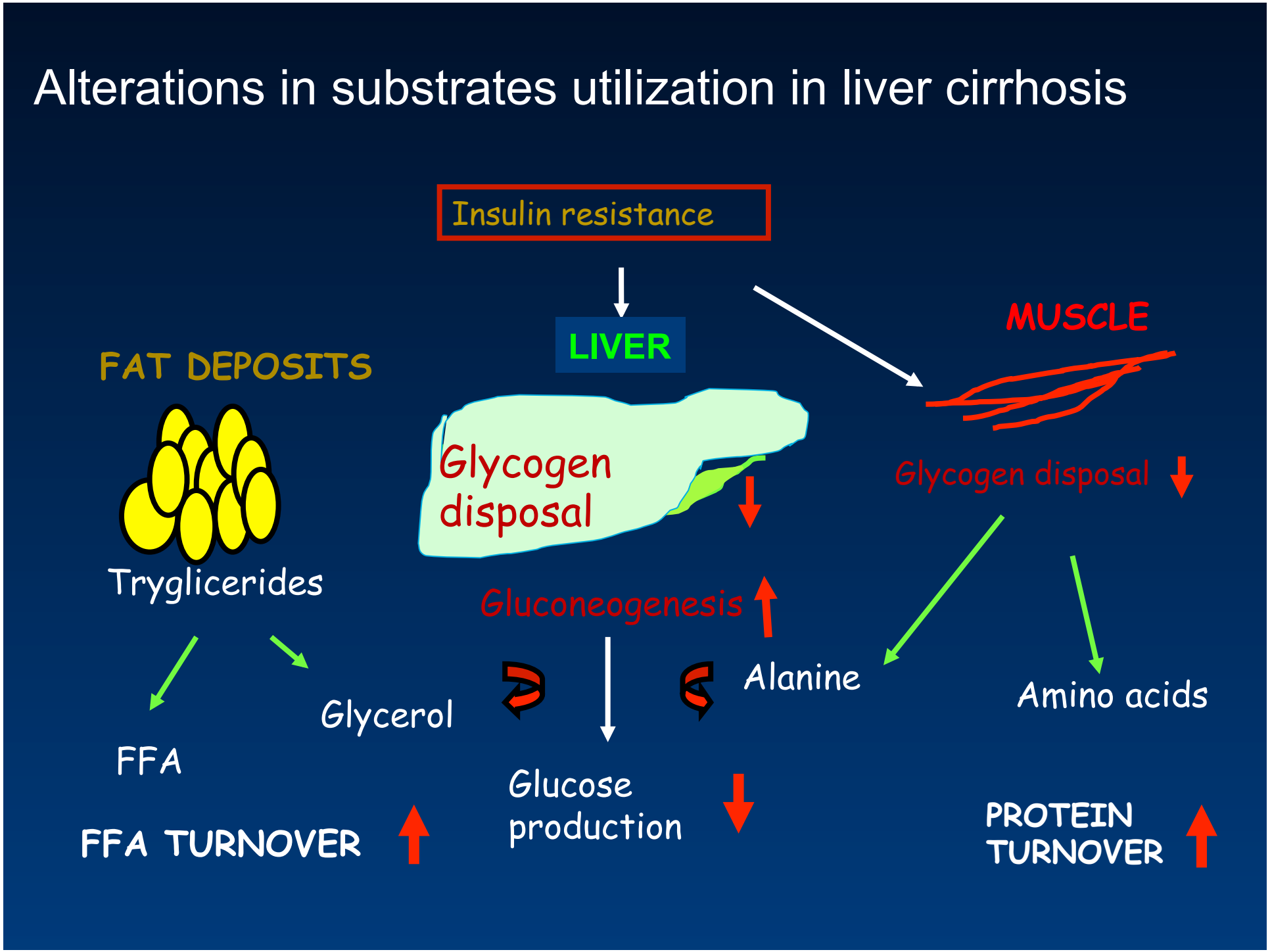
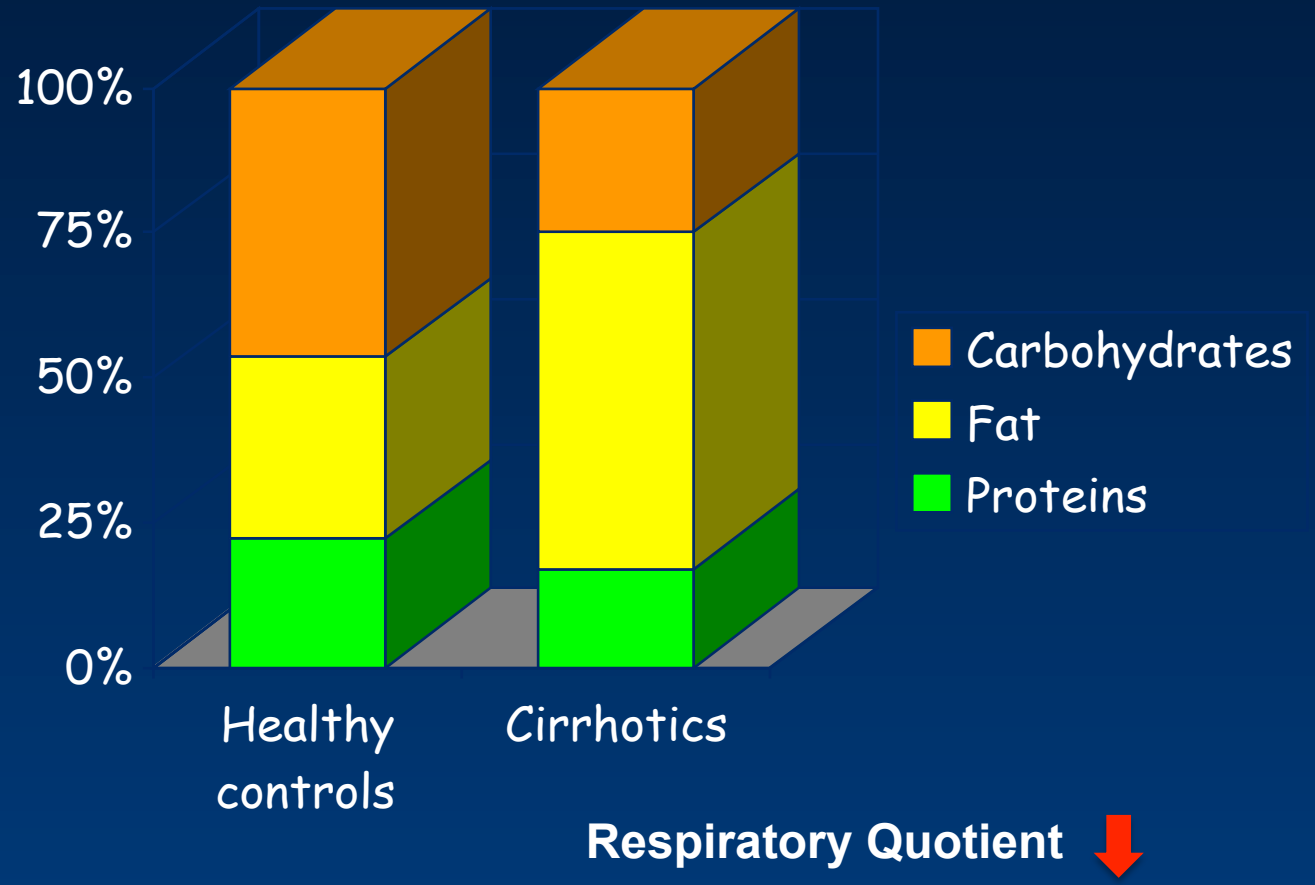
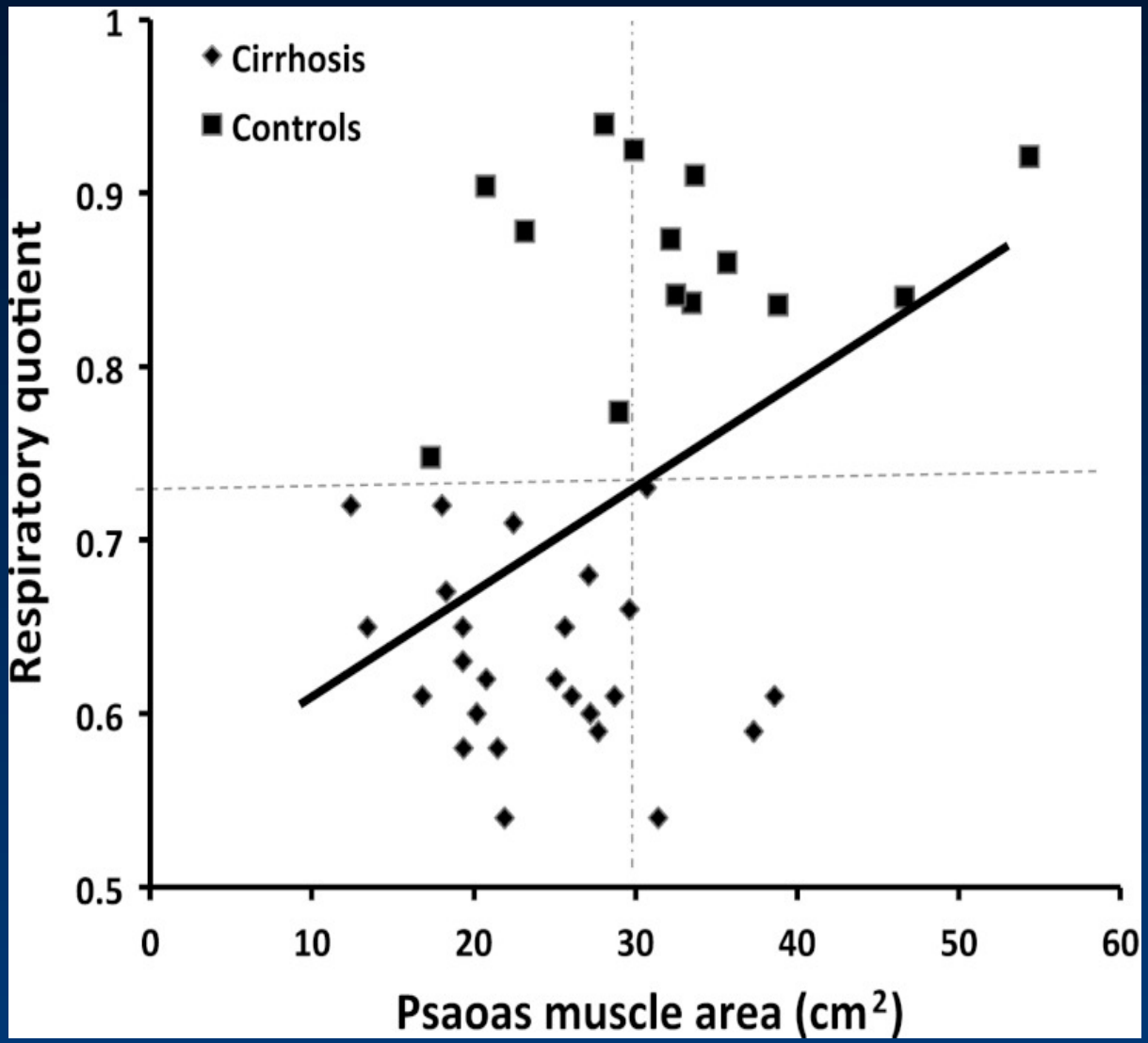
Alterations in substrates utilization in liver cirrhosis



Substrates oxidation in cirrhotic patients and in healthy controls in the postabsorptive state

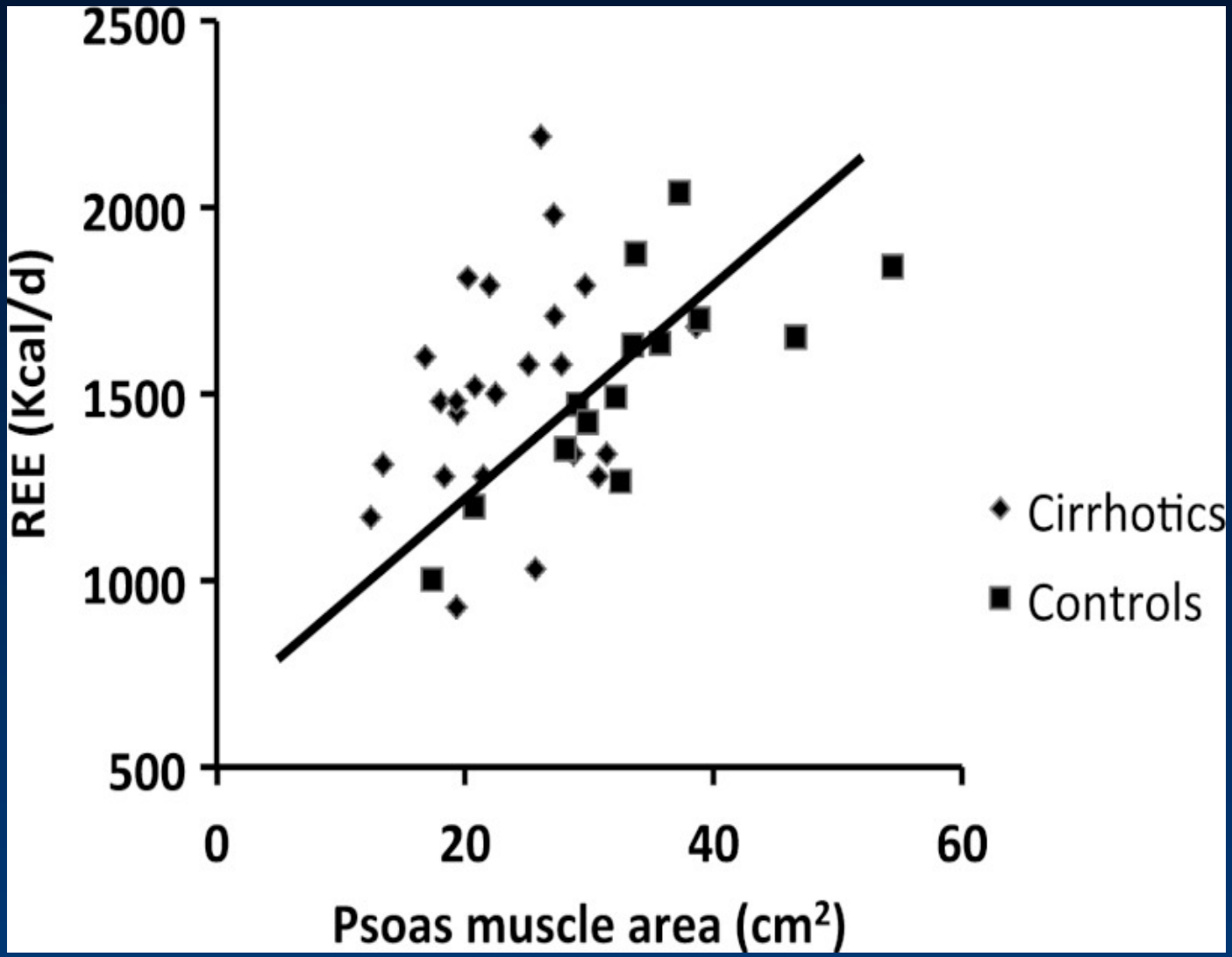


RQ is directly correlated with psoas muscle area



Glass C et al J Appl Physiol 2013

REE is directly correlated with psoas muscle area



Glass C et al J Appl Physiol

Some practical advice for patients

- Food intake and life style are very important in liver diseases
- You should always report the doctor any relevant changes in food intake
- If you need advise for food intake the doctor will help you and suggest a dietician

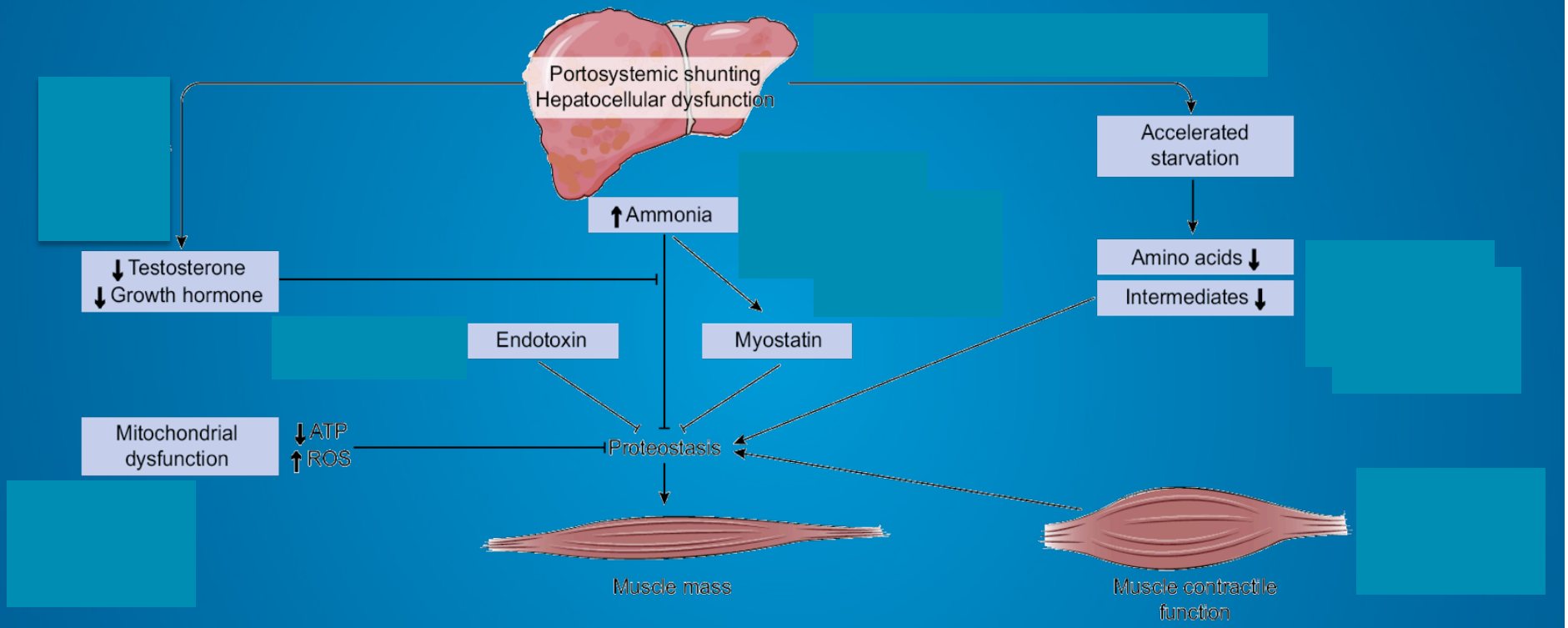
- Reduce periods of starvation

Main meals should be breakfast, lunch and dinner

but also snacks may be advisable

  - late-evening snack is the most important

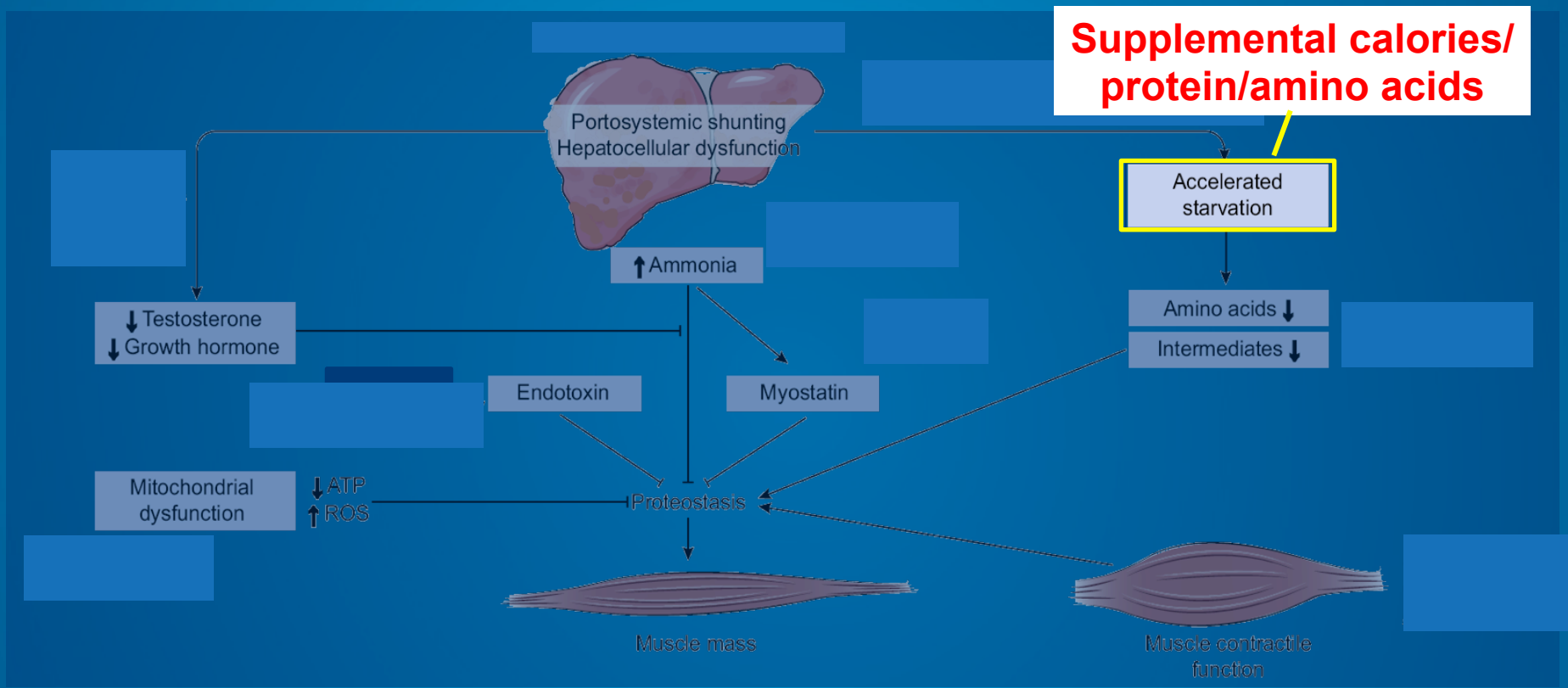
Mechanisms resulting in sarcopenia



- Anabolic resistance and dysregulated proteostasis result in sarcopenia and/or failure to respond to standard supplementation
- These mechanisms represent potential therapeutic targets

Figure adapted from Dasarathy S. Curr Opin Gastroenterol 2016;32:159–65
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

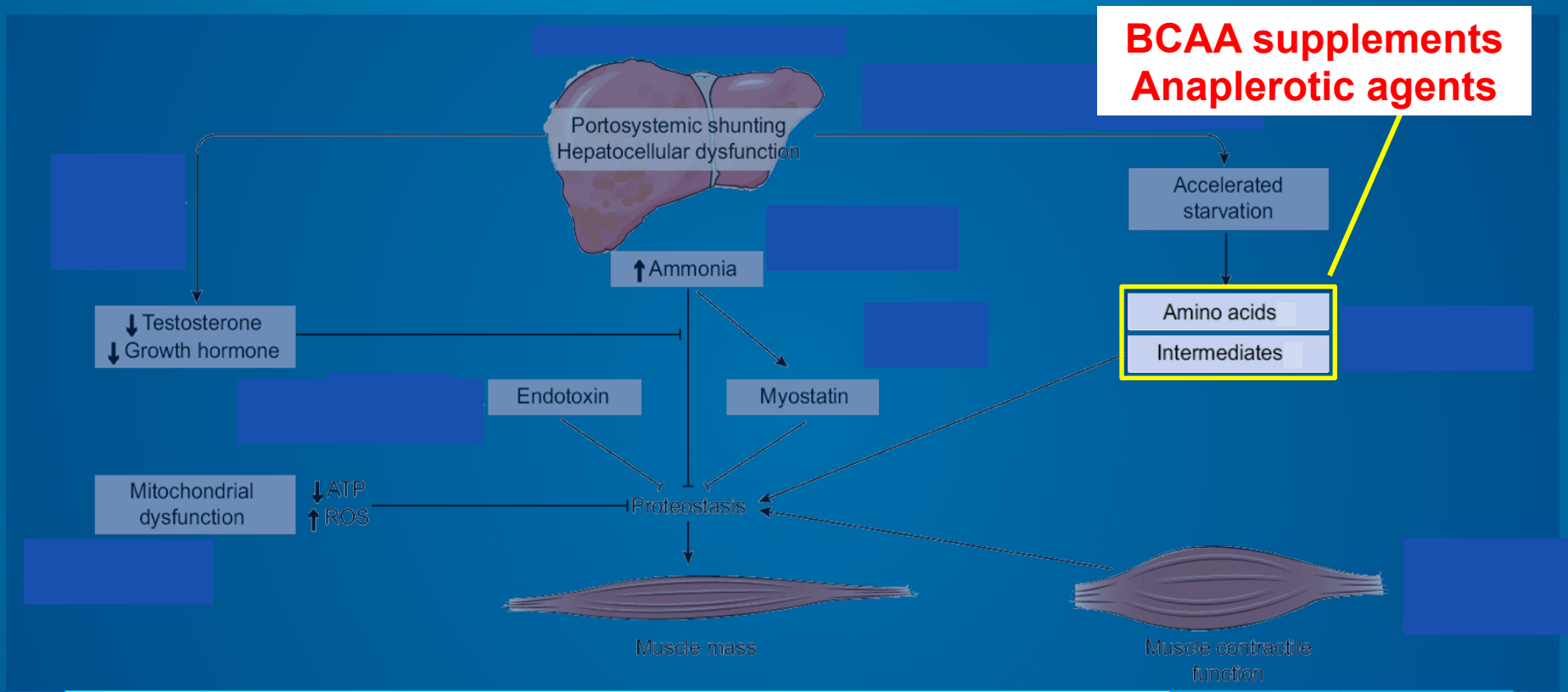
Potential management approaches to sarcopenia: Oral supplements



Recommendations		
Include late evening oral nutritional supplementation (ONS) and breakfast in the dietary regimen of malnourished patients with decompensated cirrhosis	II-1 B	1

Figure adapted from Dasarathy S. Curr Opin Gastroenterol 2016;32:159–65
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

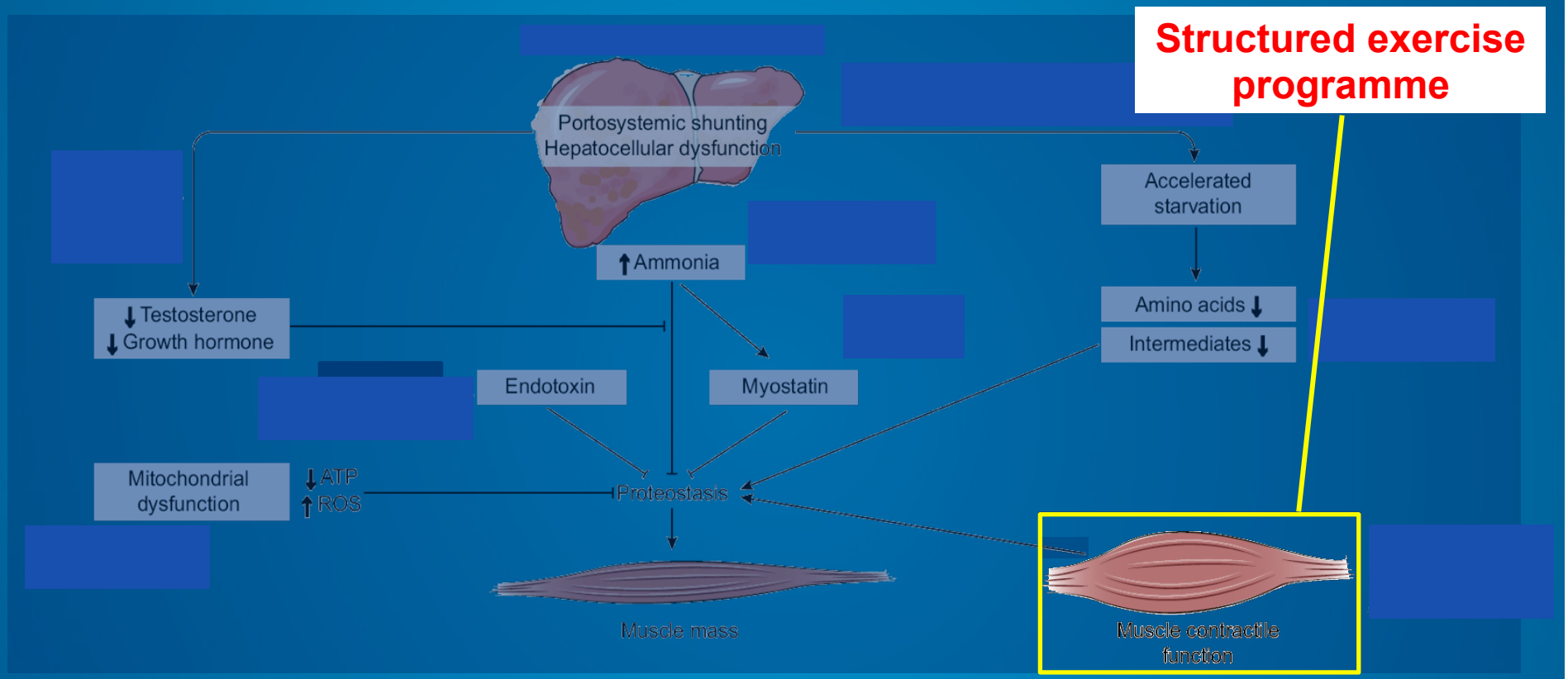
Potential management approaches to sarcopenia: BCAA supplements and anaplerotic agents



Recommendations	Grade of evidence	Grade of recommendation
BCAA supplements and leucine-enriched amino acid supplements should be considered in patients with decompensated cirrhosis when adequate nitrogen intake is not achieved by oral diet	II-1 C	1

Figure adapted from Dasarathy S. Curr Opin Gastroenterol 2016;32:159–65
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Potential management approaches to sarcopenia: Exercise



Recommendations	Grade of evidence	Grade of recommendation
Avoid hypomobility in patients with cirrhosis whenever possible, and progressively increase physical activity to prevent and/or ameliorate sarcopenia	II-1 C	2

Figure adapted from Dasarathy S. Curr Opin Gastroenterol 2016;32:159–65
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Potential management approaches to sarcopenia: Other approaches

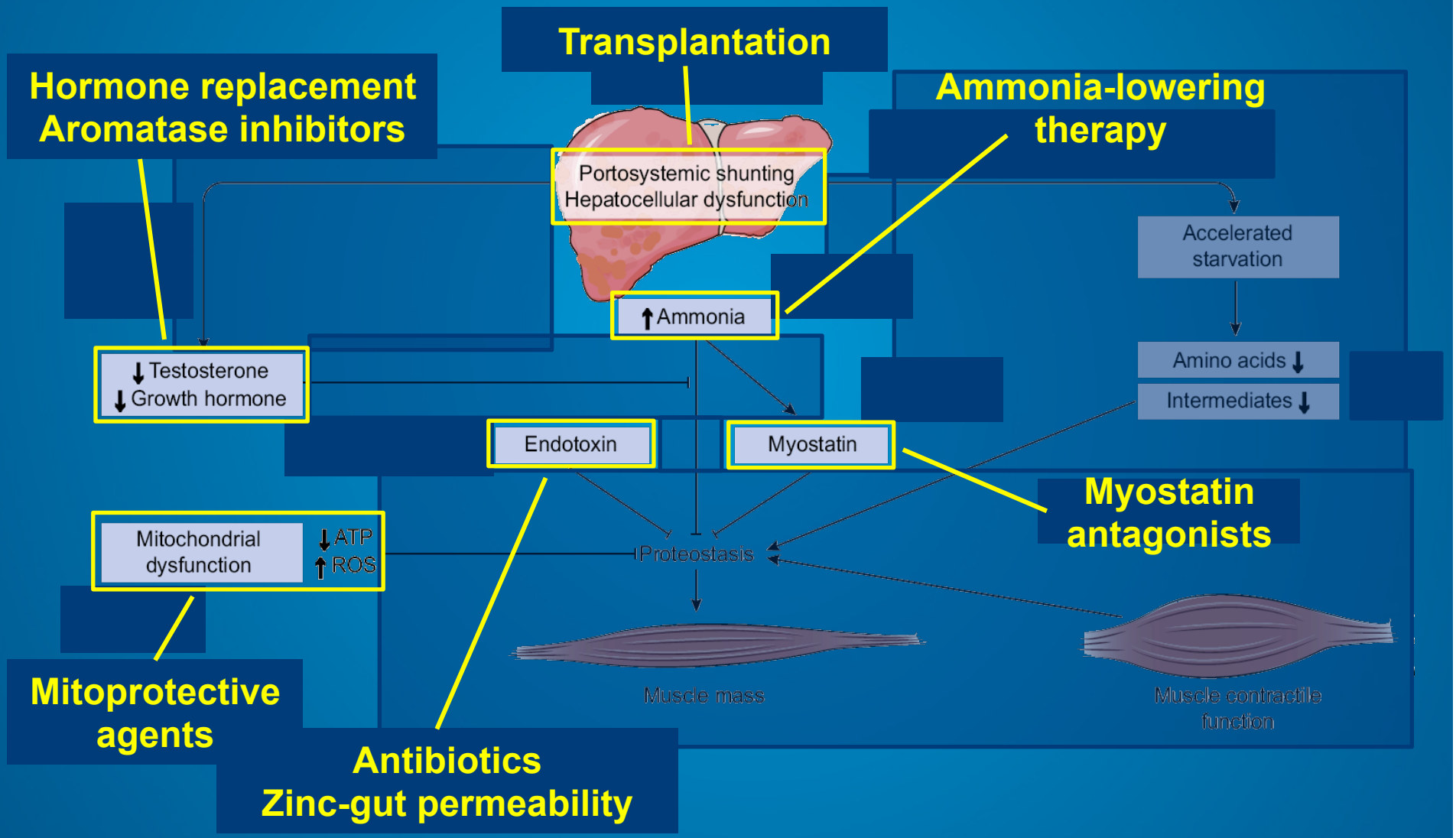
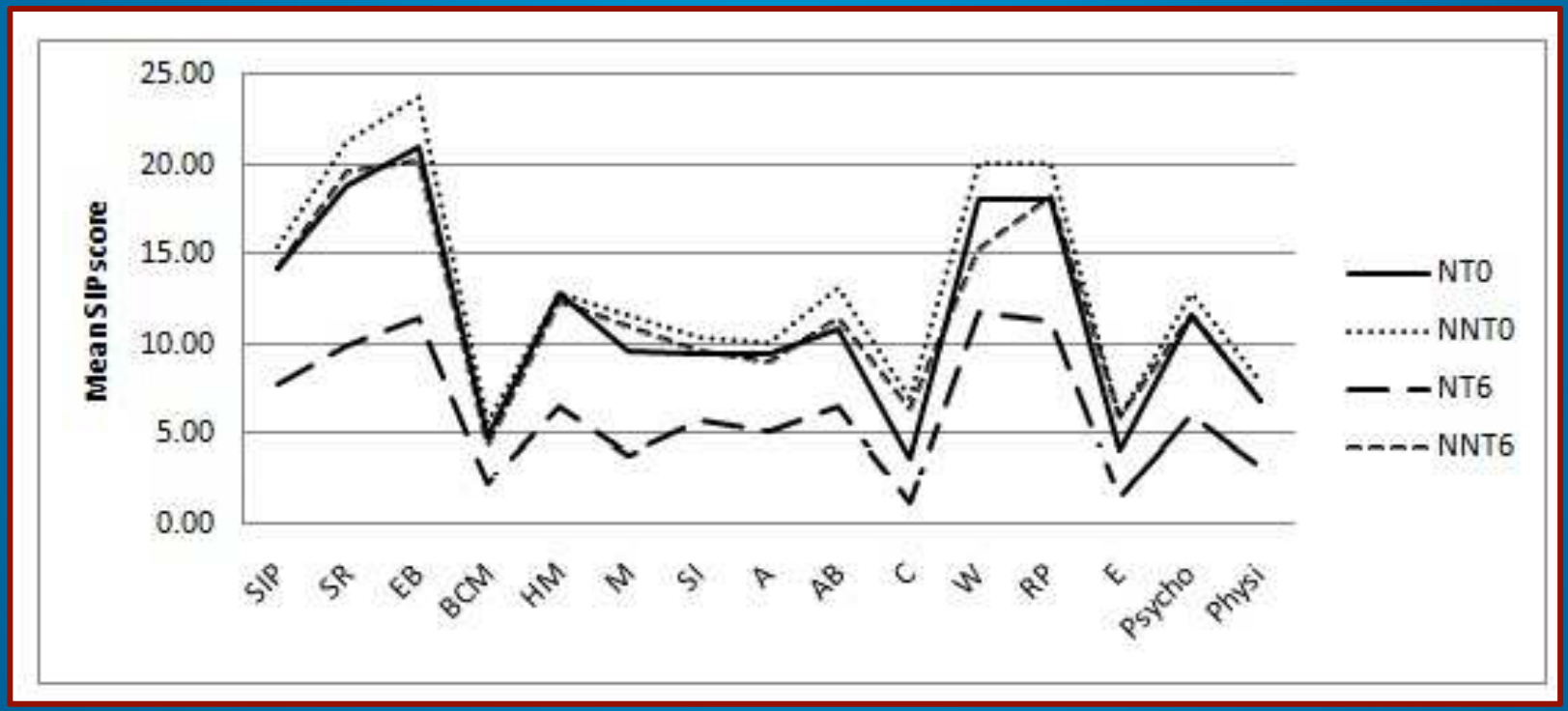


Figure adapted from Dasarathy S. Curr Opin Gastroenterol 2016;32:159–65
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Nutritional approach to sarcopenia in patients with cirrhosis

Oral nutritional therapy, following standard guidelines, vs continuing the same diet, for 6 months, was able to improve MHE, lower OHE episodes , ameliorate SIP score in a randomized controlled trial.



1. Maharshi S, et al. Clin Gastroenterol Hepatol 2016;14:454–60;
2. EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Obesity in cirrhosis: Assessment and interpretation

- Sedentary lifestyles are highly prevalent in patients with cirrhosis, increasing obesity risk, but obesity does not rule out malnutrition. Obesity is present in most cases of NASH-related cirrhosis
- Estimate and treat nutrition alterations in obese patients with cirrhosis (BMI >30 kg/m^2 in absence of fluid retention)

Recommendations	Grade of evidence	Grade of recommendation
In the diagnosis of obesity (BMI >30 kg/m^2) always consider the confounding effect of fluid retention. Estimate dry body weight, although accuracy is low	II-2 B	2

Nutritional management principles in cirrhosis: Approach and management of obesity

- Multiple studies suggest a reduction in body weight improves outcomes in obese patients with compensated cirrhosis[1–3]
- Weight loss can be achieved by nutritional therapy and supervised moderate-intensity physical exercise tailored to the patient's ability

Recommendations	Grade of evidence	Grade of recommendation
Implement a nutritional and lifestyle programme to achieve progressive weight loss (≥5–10%) in obese patients with cirrhosis (BMI >30 kg/m^2 corrected for water retention)	II-2 C	1
Adopt a tailored, moderately hypocaloric (-500–800 kcal/day) diet, including an adequate amount of protein (>1.5 g protein/kg ideal BW/day) to achieve weight loss without compromising protein stores in obese patients with cirrhosis	II-1 C	2

1. Zenith L, et al. Clin Gastroenterol Hepatol 2014;12:e1922; 2. Everhart JE, et al. Gastroenterology 2009;137:549–57;
3. Macias-Rodriguez RU, et al. Clin Transl Gastroenterol 2016;7:e180
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Nutritional treatment options for hepatic encephalopathy

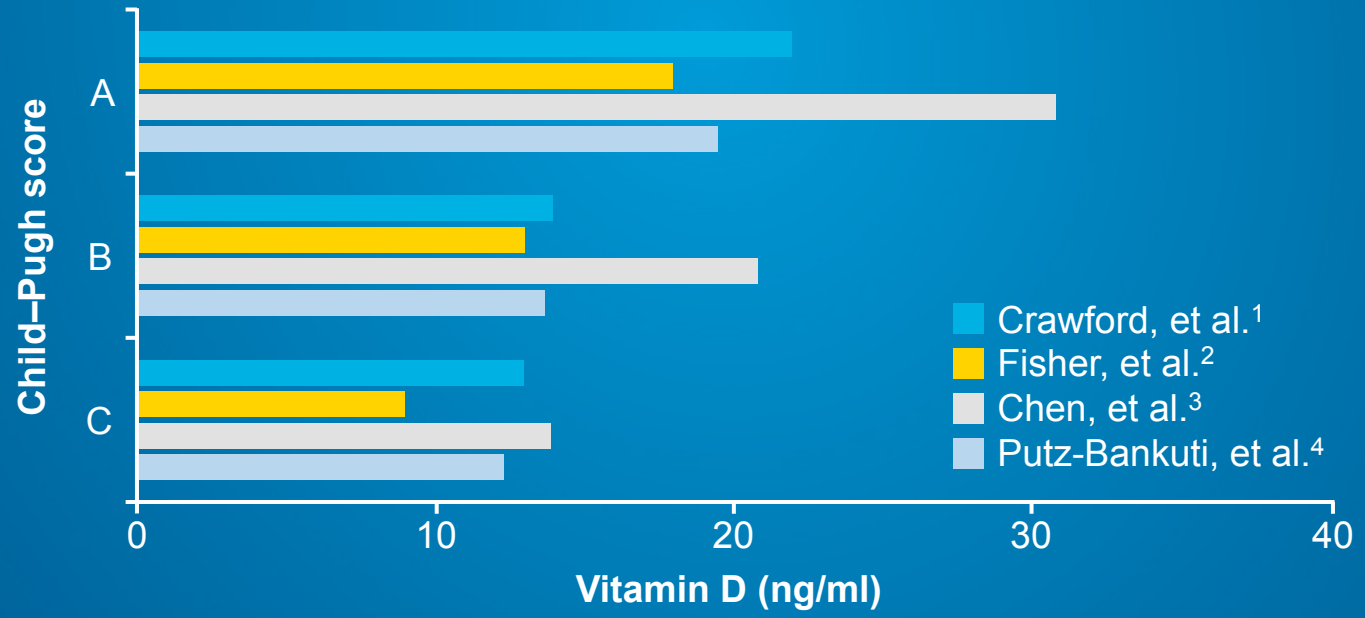
Recommendations	Grade of evidence	Grade of recommendation
Nutritional status and sarcopenia should be evaluated in patients with HE	II-3 B	1
Avoid protein restriction in patients with HE	II-1 A	1
Optimal daily protein and energy intake should not be lower than the general recommendations for patients with cirrhosis	II-1 A	1
Encourage the consumption of vegetables and dairy protein	II-3 B	1
BCAA supplementation should be considered to improve neuropsychiatric performance and to reach the recommended nitrogen intake	I-1 A	1
Oral dietary intake is preferred in patients who can tolerate it. In patients with grade III–IV encephalopathy who are unable to eat, provide nutrition by nasogastric tube (in patients with protected airways) or parenterally	II-1 B	1

1. McDaniel J, et al. Am J Physiol Gastrointest Liver Physiol 2016;310:G163–70
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Micronutrients

- Vitamin deficiencies in liver disease are generally related to hepatic dysfunction and diminished reserves
  - Inadequate dietary intake and malabsorption increase with disease severity

Serum 25(OH)D concentrations in patients with cirrhosis, stratified by Child–Pugh score in four individual studies[1–4]



1. Crawford BAL, et al. Osteoporos Int 2003;14:987–94; 2. Fisher L, et al. Clin Gastroenterol Hepatol 2007;5:513–20;
3. Chen CC, et al. J Gastroenterol Hepatol 1996;11:417–21; 4. Putz-Bankuti C, et al. Liver Int 2012;32:845–51
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Micronutrients

- A majority of liver disease patients considered for liver transplantation present with vitamin A and D deficiencies
  - Vitamin D levels <20 ng/ml are reported in chronic cholestatic conditions, and often inversely correlate with disease severity and Child–Pugh score
  - Vitamin D also correlates with treatment response in HCV, NAFLD and patients who develop HCC

Recommendations	Grade of evidence	Grade of recommendation
In patients with cirrhosis, administer micronutrients and vitamins to treat confirmed or clinically suspected deficiency	II-1 C	1
Assess vitamin D levels in patients with cirrhosis as deficiency is highly prevalent and may adversely affect clinical outcomes	II-3 B	1
Supplement vitamin D orally in patients with cirrhosis and vitamin D levels <20 ng/ml, to reach serum vitamin D (25(OH)D) >30 ng/ml	II-1 B	1

Micronutrients

- Hyponatraemia is common in patients with cirrhosis, and more likely when sodium intake is low with water unchanged or increased. Careful monitoring of sodium and water intake is required
- Confirmed or clinically suspected micronutrient deficiencies should be treated based on accepted general recommendations and common practice

Recommendations	Grade of evidence	Grade of recommendation
In patients with cirrhosis and ascites under sodium restriction (recommended intake of sodium ~80 mmol day = 2 g of sodium corresponding to 5 g of salt added daily to the diet according to EASL guidelines) take care to improve diet palatability as this may cause a reduction in calorie intake	II-2 B	1

Nutritional treatment options in patients with cirrhosis and bone disease – risk factors

- ~30% patients with chronic liver disease, and 30% eligible for liver transplantation have osteoporosis, with higher prevalence in cholestasis
  - Characterized by loss of bone mass and quality, causing fragility fractures

Risk factors for osteoporosis in chronic liver disease

- Male hypogonadism
- Alcohol abuse
- Smoking
- BMI <19 kg/m^2
- Early menopause

- Family history of osteoporotic fracture
- Treatment with corticosteroids*
- Advanced age
- Secondary amenorrhoea >6 months

*≥5 mg/d prednisone for ≥3 months

EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Nutritional treatment options in patients with cirrhosis and bone disease – diagnosis

- According to the WHO, bone densitometry of the lumbar spine and hip is the gold standard for diagnosis of osteoporosis and osteopenia
  - Should be evaluated in:
    - Patients with previous fragility fractures
    - Those treated with corticosteroids
    - Before liver transplantation
    - In cholestatic diseases
    - Patients with cirrhosis

Recommendations	Grade of evidence	Grade of recommendation
Evaluate BMD in patients with cirrhosis, cholestatic liver disease, receiving long-term corticosteroid treatment, and before liver transplantation	II-2 A	1
Utilize lumbar and femoral densitometry (DEXA) for diagnosing osteoporosis and osteopenia. Use lateral X-rays of dorsal and lumbar spine for diagnosing vertebral fractures	II-3 A	1
Repeat DEXA after 2–3 years in patients within normal BMD, and within 1 year when rapid bone loss is expected	II-1 B	1

Nutritional treatment options in patients with cirrhosis and bone disease – treatment

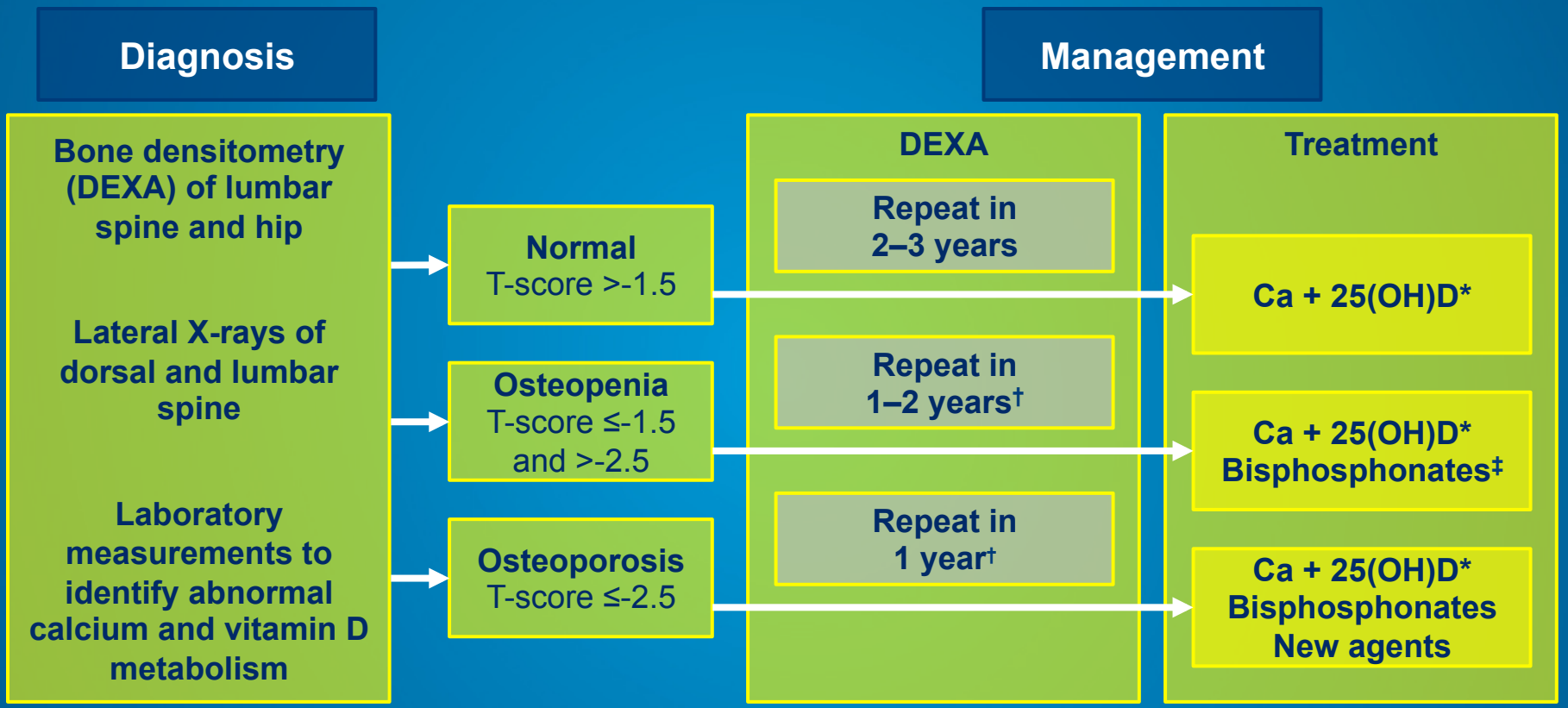
- A balanced diet is recommended
  - Including calcium and 25(OH)D supplements to preserve normal levels
- Physical activity is recommended
  - Especially exercises to improve mechanics of the spine
- Factors that increase bone loss (alcohol, tobacco, corticosteroids etc.) should be minimized
- Although studies are limited, bisphosphonates* are reported to increase bone mass in patients with PBC with no serious adverse events[1,2]

Recommendations	Grade of evidence	Grade of recommendation
Include supplements of calcium (1,000–1,500 mg/day) and 25(OH)D (400–800 IU/day or 260 µg every 2 weeks) in patients with chronic liver disease and a T-score below -1.5	II-3 A	1
Utilize bisphosphonates in patients with cirrhosis and osteoporosis, and in those waiting for liver transplantation	I A	1
Consider testosterone supplementation and venesection in males with haemochromatosis and hypogonadism	II-2 B	1

*Including etidronate, alendronate, and ibandronate

1. Guanabens N, et al. Am J Gastroenterol 2003;98:2268–74; 2. Guanabens N, et al. Hepatology 2013;58:2070–8
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Diagnosis and management of bone disease in patients with chronic liver disease – summary



*Calcium (1,000–1,500 mg/d) and 25-hydroxy-vitamin D (400–800 IU/day or 260 µg every 2 weeks) to preserve normal levels;
†According to the severity of liver disease and cholestasis, and in patients taking corticosteroids;
‡Depending on additional risk factors
EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Malnutrition in patients undergoing liver surgery and liver transplantation – preoperative nutrition

- Patients with severe undernutrition* or obesity† undergoing liver surgery have higher risk of morbidity and mortality
- Liver glycogen is depleted in patients with cirrhosis
  - Periods without nutrient intake should be reduced

*BMI <18.5 kg/m^2; †BMI >40 kg/m^2

EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Malnutrition in patients undergoing liver surgery and liver transplantation – preoperative nutrition

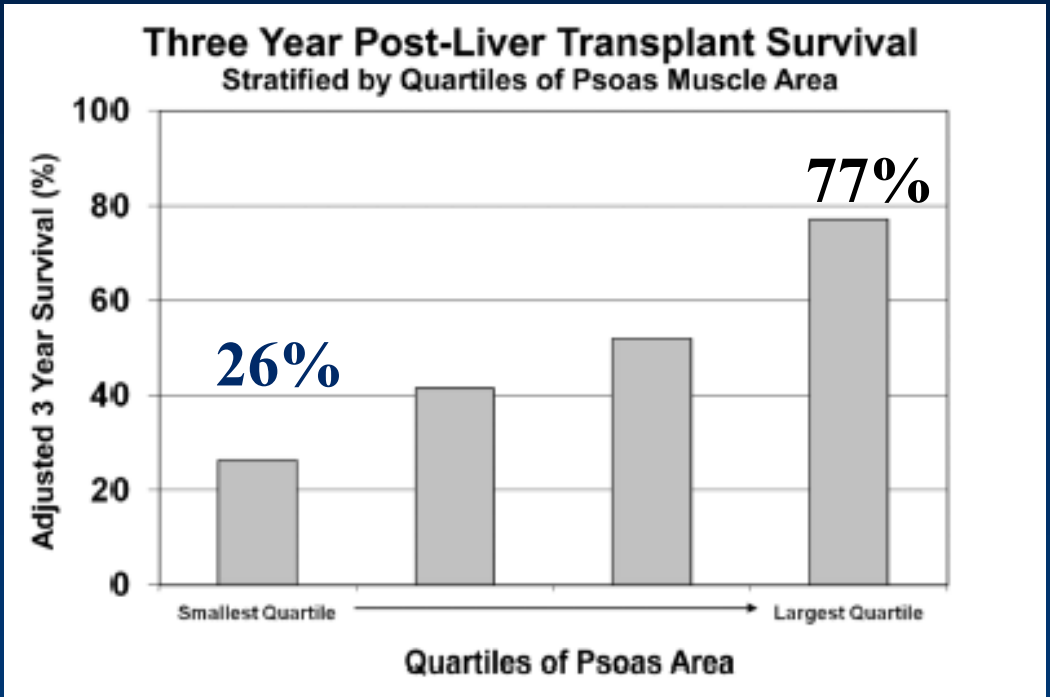
Recommendations	Grade of evidence	Grade of recommendation
Screen for malnutrition and sarcopenia in patients with cirrhosis listed for LT or scheduled for elective surgery. Treat sarcopenia prior to elective surgery, to enable improvement in body protein status and clinical outcomes	III B	2
Screen for sarcopenic obesity with body composition analysis in obese patients with cirrhosis considered for surgery	III C	2
If treatment goal is *maintenance* of nutritional status, plan: • Total energy intake 30 kcal/kg.BW/day and protein intake 1.2 g/ kg.BW/day If treatment goal is *improvement* of nutritional status, plan: • Total energy intake 35 kcal/kg.BW/day and protein intake 1.5 g/ kg.BW/day	II-3 B	1
Utilize standard nutrition regimens. Specialized regimens (e.g. BCAA-enriched, immune-enhancing diets) have not been shown to improve morbidity or mortality	II-1 B	1

*BMI <18.5 kg/m^2; †BMI >40 kg/m^2

EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

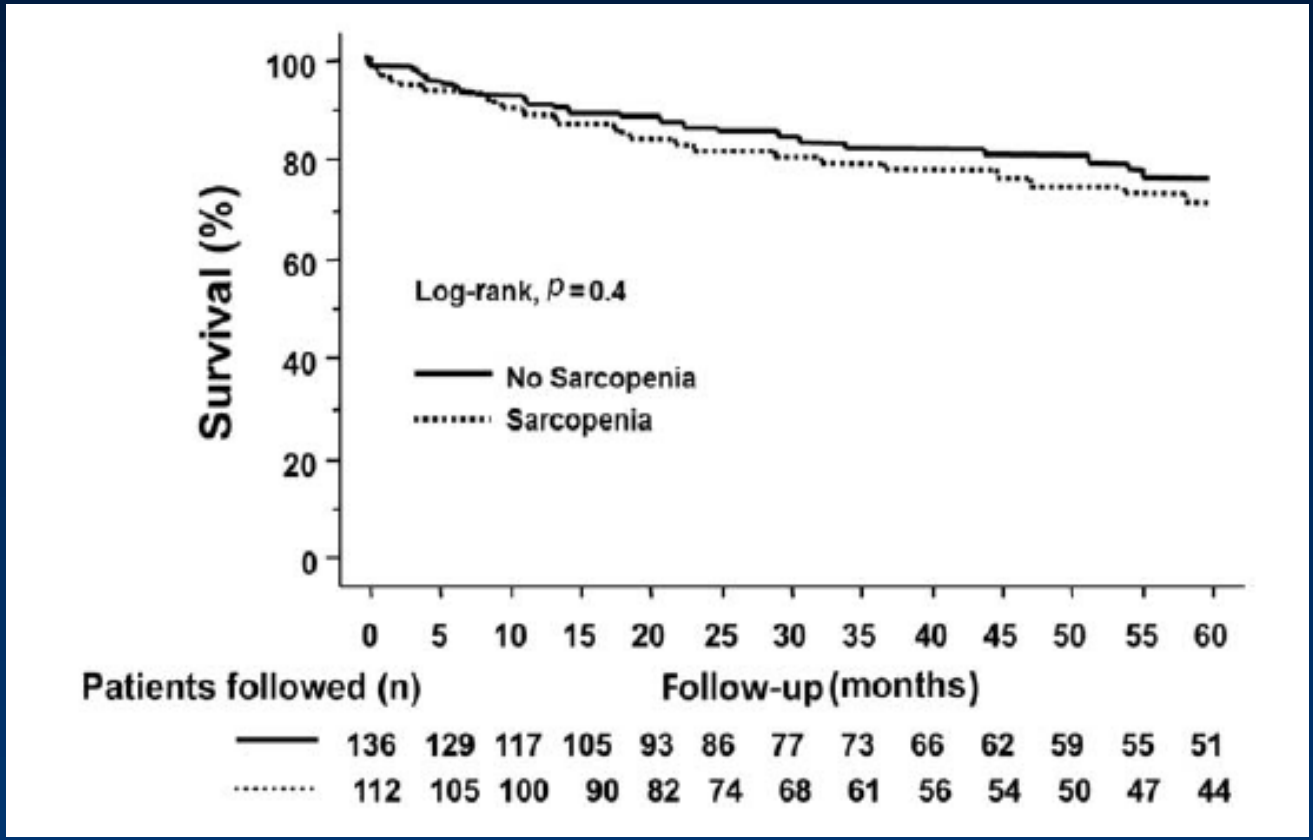
Muscle wasting is associated with higher post liver transplant mortality

By measuring the cross-sectional area of the psoas muscle (PA) on CT scans in 163 liver transplant recipients, a strong association was found between the psoas area and post-transplant mortality (HR=3.7 per 1000 mm^2 decrease in the PA; $p<0.0001$).



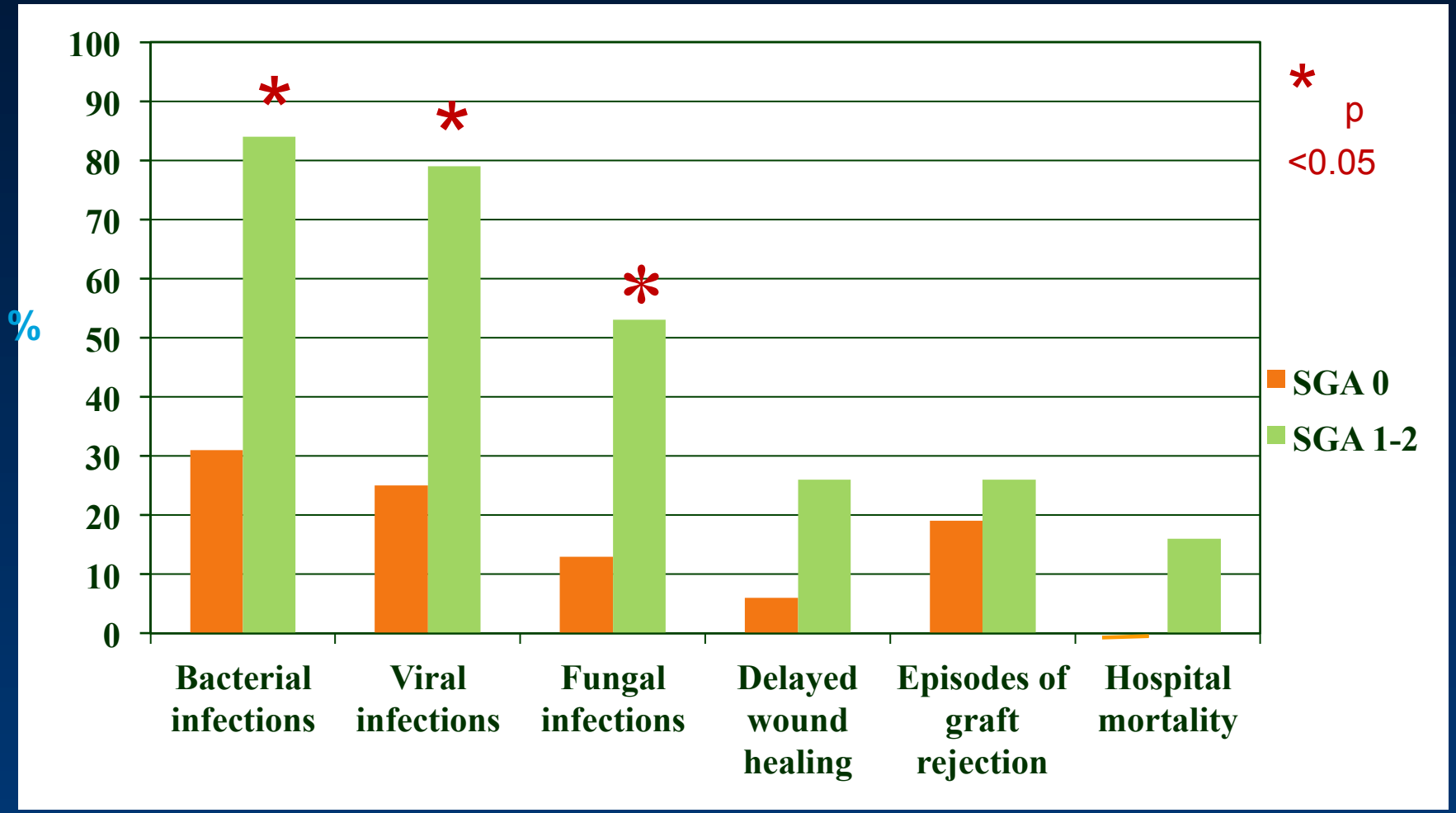
Englesbe MJ, J Am Coll Surg 2010

Muscle wasting is not associated with higher post liver transplant mortality



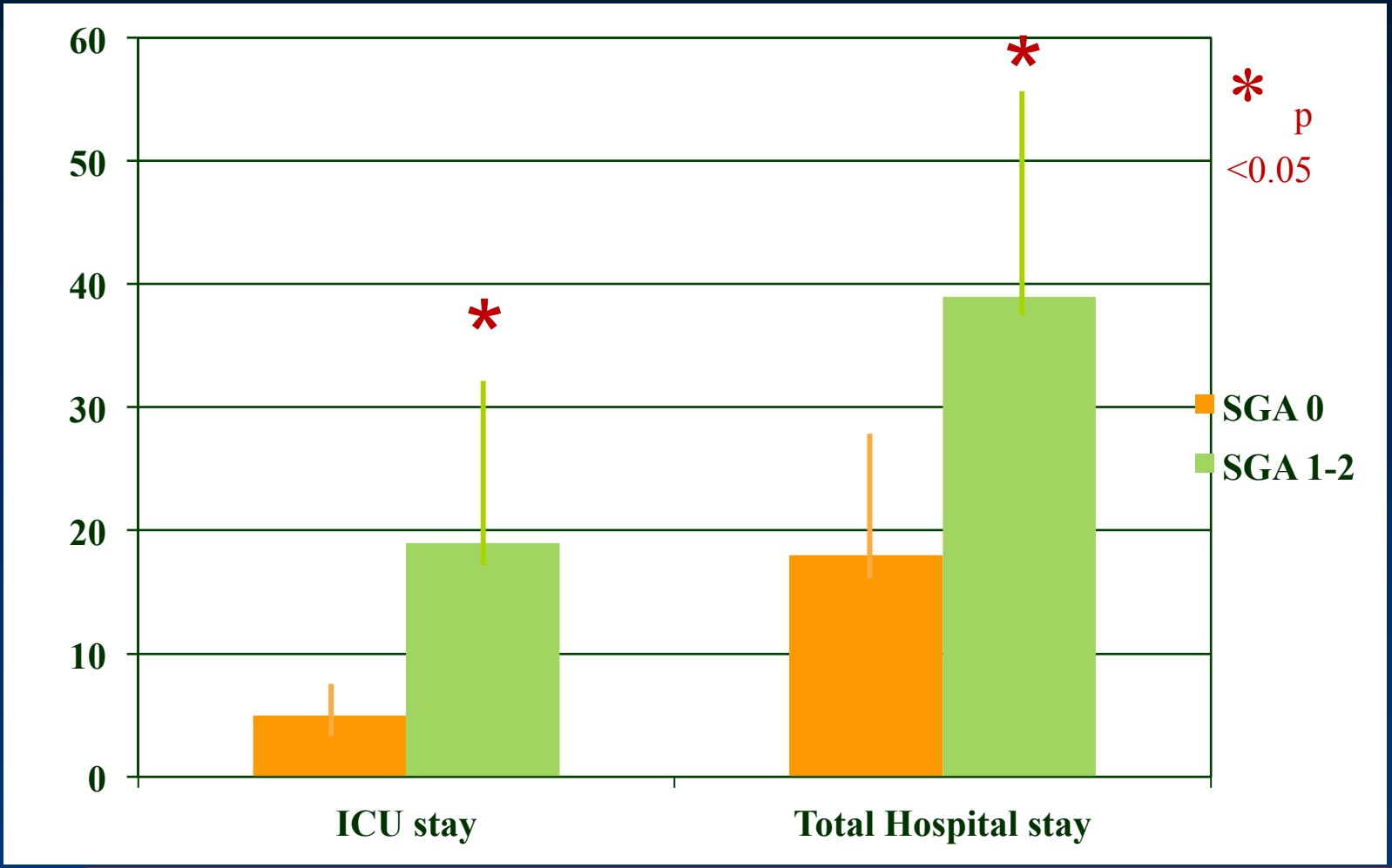
Montano-Loza AJ, liver transplant 2014

More in-hospital infections after liver transplantation according to the nutritional status



Merli M Liv Int 2010

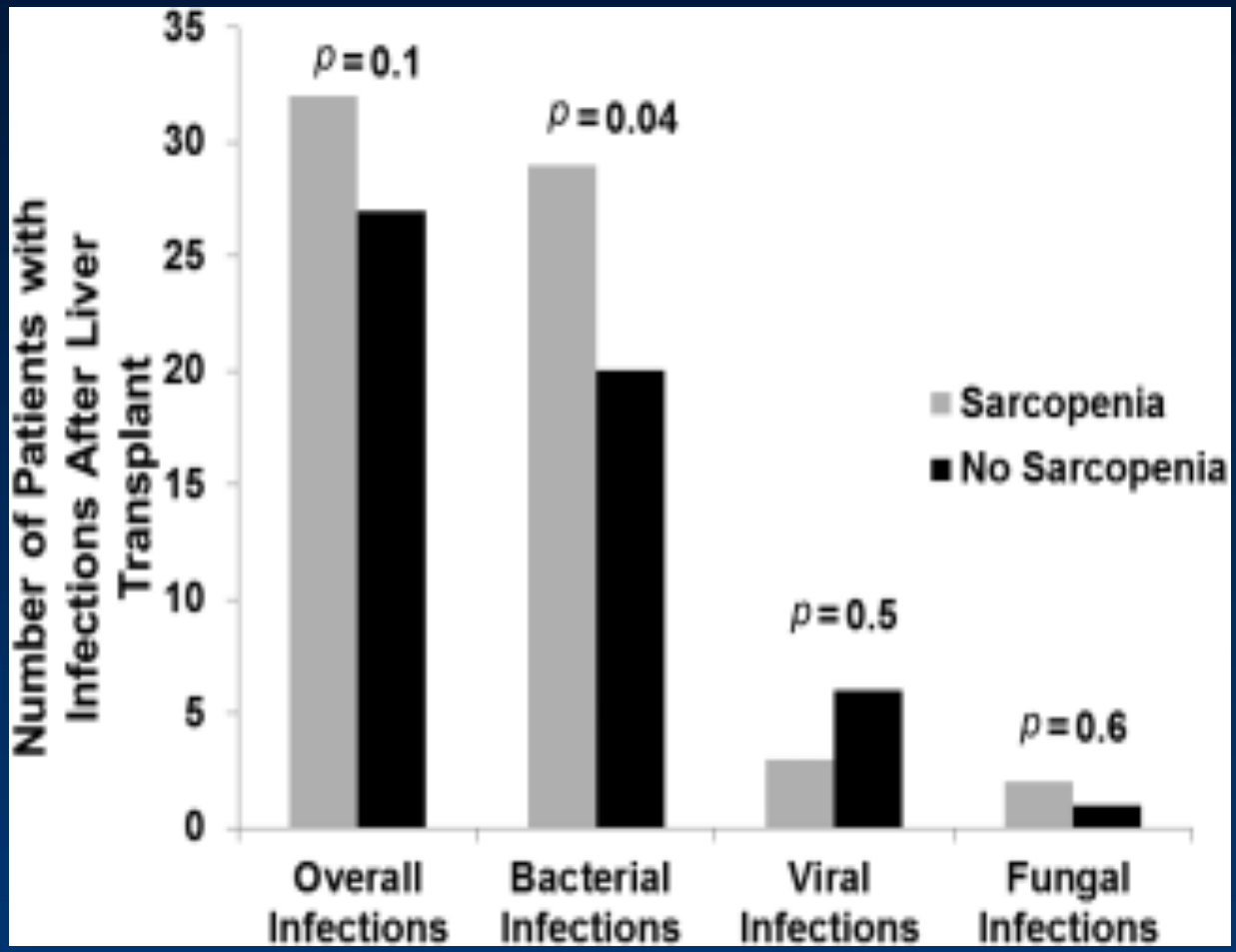
Longer hospital stay after liver transplantation according to the nutritional status



Nutrition was selected as independent predictor in multivariate analysis

Merli M Liv Int 2010

Severe muscle depletion predicts postoperative infections after liver transplantation



90 days follow up

Montano Loza 2014

SHOULD WE:

REFUSE
ANTICIPATE
POSTICIPATE
MALNOURISHED SARCOPENIC CIRRHOTIC PATIENTS FOR LIVER TRANSPLANTATION?

Malnutrition in patients undergoing liver surgery and liver transplantation – postoperative nutrition

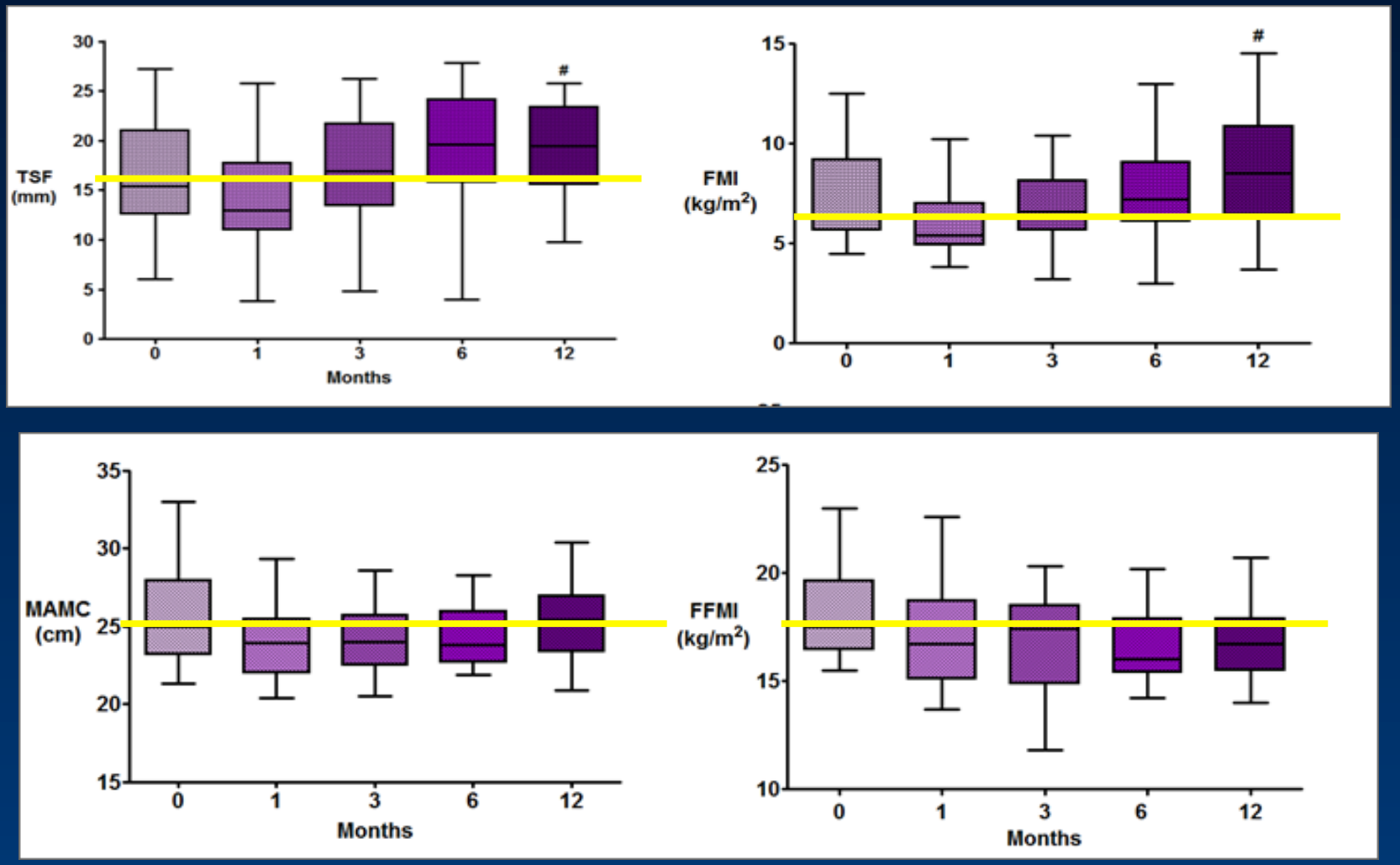
- Versus fluid and electrolytes only, post-operative nutrition decreases:
  - Ventilator time
  - Length of ICU stay
  - Bacterial and viral infections
  - Bile duct and other complications

Recommendations	Grade of evidence	Grade of recommendation
After LT, initiate normal food and/or enteral tube feeding within 12–24 hours, or as soon as possible, to reduce infection rates	II-2 B	1
When oral or enteral nutrition are not possible, parenteral nutrition should be used over not feeding	II-2 B	1
After the acute postoperative phase, provide an energy intake of 35 kcal/kg.BW/day and protein intake of 1.5 g/kg.BW/day	II-2 C	1
After other surgical procedures, manage patients with chronic liver disease according to ERAS protocols	III C	2
Consider parenteral nutrition in patients with unprotected airways and HE when cough and swallow reflexes are compromised, or enteral nutrition is contraindicated or impractical	II-2 C	1

Malnutrition in patients undergoing liver surgery and liver transplantation – postoperative nutrition

- Patients remain in negative nitrogen balance after LT
  - Necessitates an increase in protein or amino acid provision
  - Nutrition improves nitrogen economy in non-transplant visceral surgery
- Chronic dilutional hyponatraemia should be carefully corrected after LT to avoid pontine myelinolysis
- Long-term LT survivors risk weight gain/obesity due to metabolic syndrome
  - dietary counselling and lifestyle measures should be used

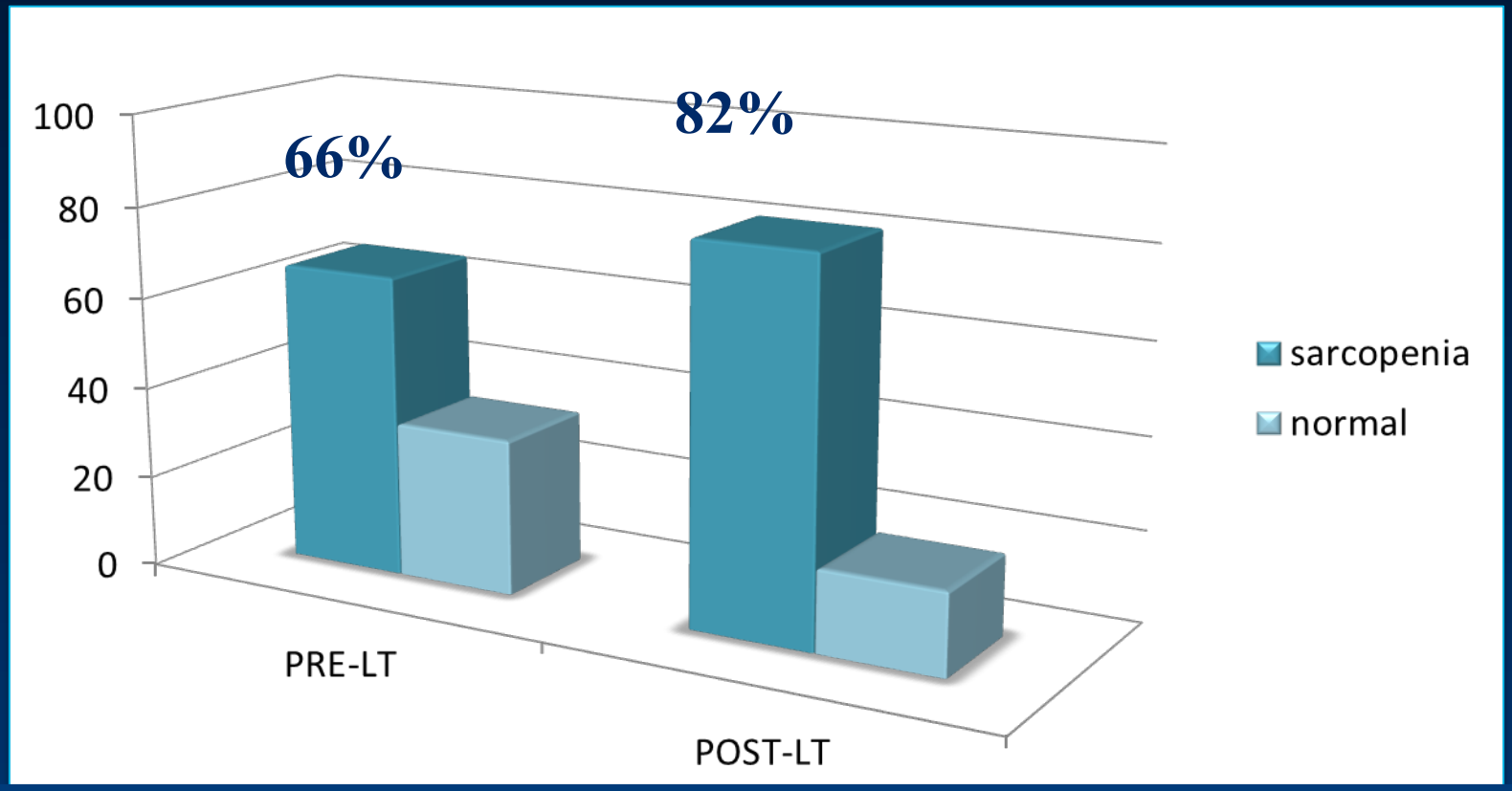
Anthropometry and DEXA before and 1, 3, 6 and 12 months after LT.



Fat-Free Mass Index (FFMI)= FFM/m^2; Fat Mass Index (FMI)= FM/m^2 ;FFM and FM were calculated by whole body DEXA scan.

Lattanzi B DLD 2013

Sarcopenia post transplant



Of the 66% of sarcopenic patients before LT, only 6% had a reversal of sarcopenia, while 15 of the 20 patients who were not sarcopenic pre-LT developed sarcopenia de novo after LT

Tsein C et Al. J Gastroenterol Hepatol 2014

Sarcopenic obesity with metabolic syndrome: a newly recognized entity following liver transplantation

Post-transplant sarcopenic obesity was present in 88% patients, and MS was present in 52% of recipients with no significant difference among etiologies.

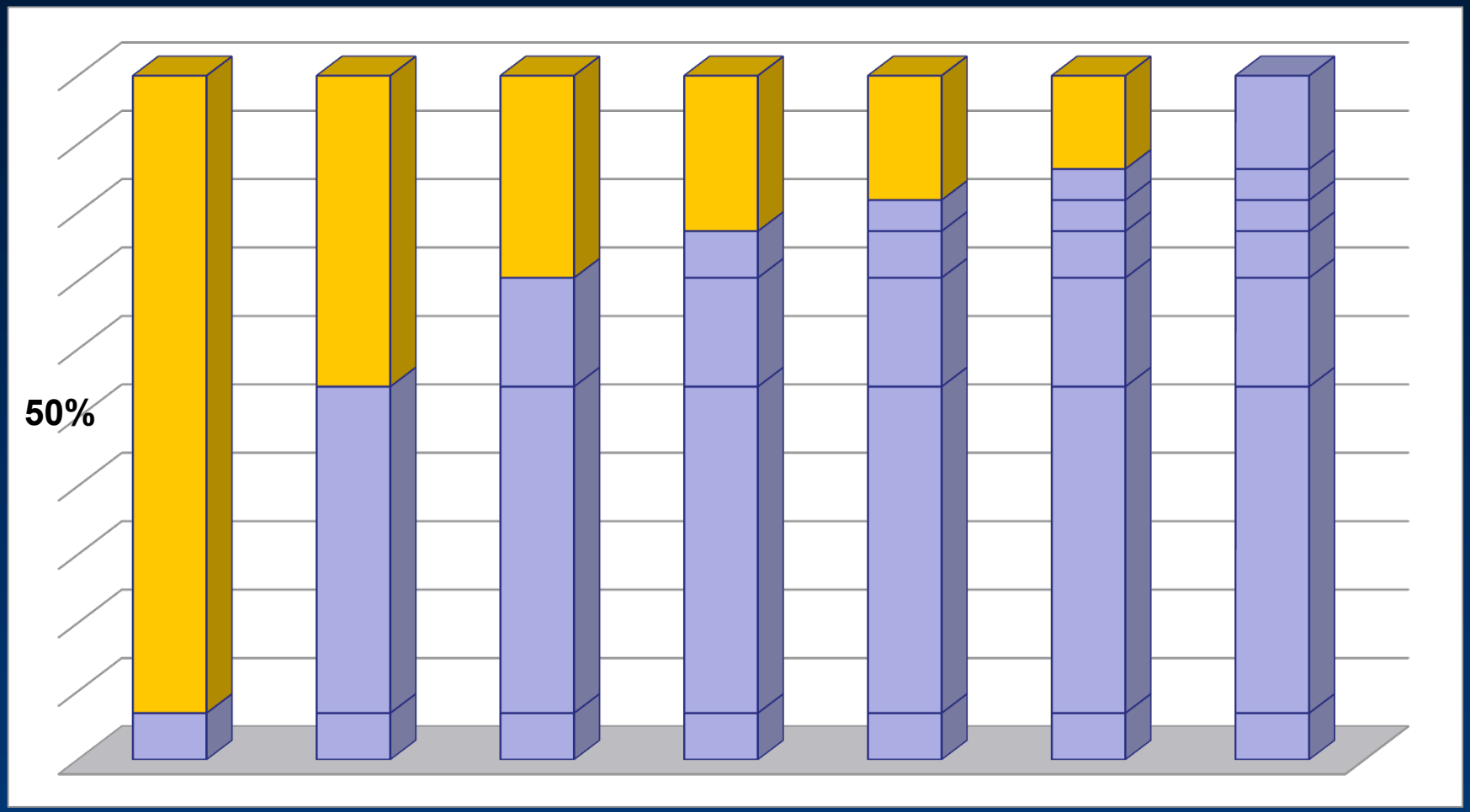
Table 2. Comparison of subjects with or without sarcopenic obesity

Parameter	No sarcopenic obesity, N = 10	Sarcopenic obesity, N = 72	p-value
BMI before transplant	20.3 ± 2.24	26.0 ± 4.0	0.008
Age at time of BIA	51.4 ± 16.7	50.1 ± 9.6	0.237
BMI at time of BIA	23.9 ± 4.6	28.2 ± 3.8	0.003
Waist circumference, cm	84.7 ± 6.7	100.5 ± 10.3	0.000
Total cholesterol, mg/dL	167.7 ± 28.7	170.5 ± 46.1	0.863
Low-density lipoprotein, mg/dL	94.7 ± 20.4	97.4 ± 36.1	0.826
Triglycerides, mg/dL	127.8 ± 56.5	151.8 ± 70.8	0.333
High-density lipoprotein, mg/dL	47 ± 9.3	45.3 ± 14.5	0.742
Diabetes, n (%)	4 (40)	42 (58)	0.321
Hypertension, n (%)	3 (30)	29 (40)	0.732
Female sex, n (%)	1 (10)	11 (15)	1.000
MS, n (%)	2 (20)	41 (57)	0.041
Number of components of MS	1 (1–2.5)	3 (2–3)	0.011

BIA, bioelectric impedance analysis; BMI, body mass index; MS, metabolic syndrome.

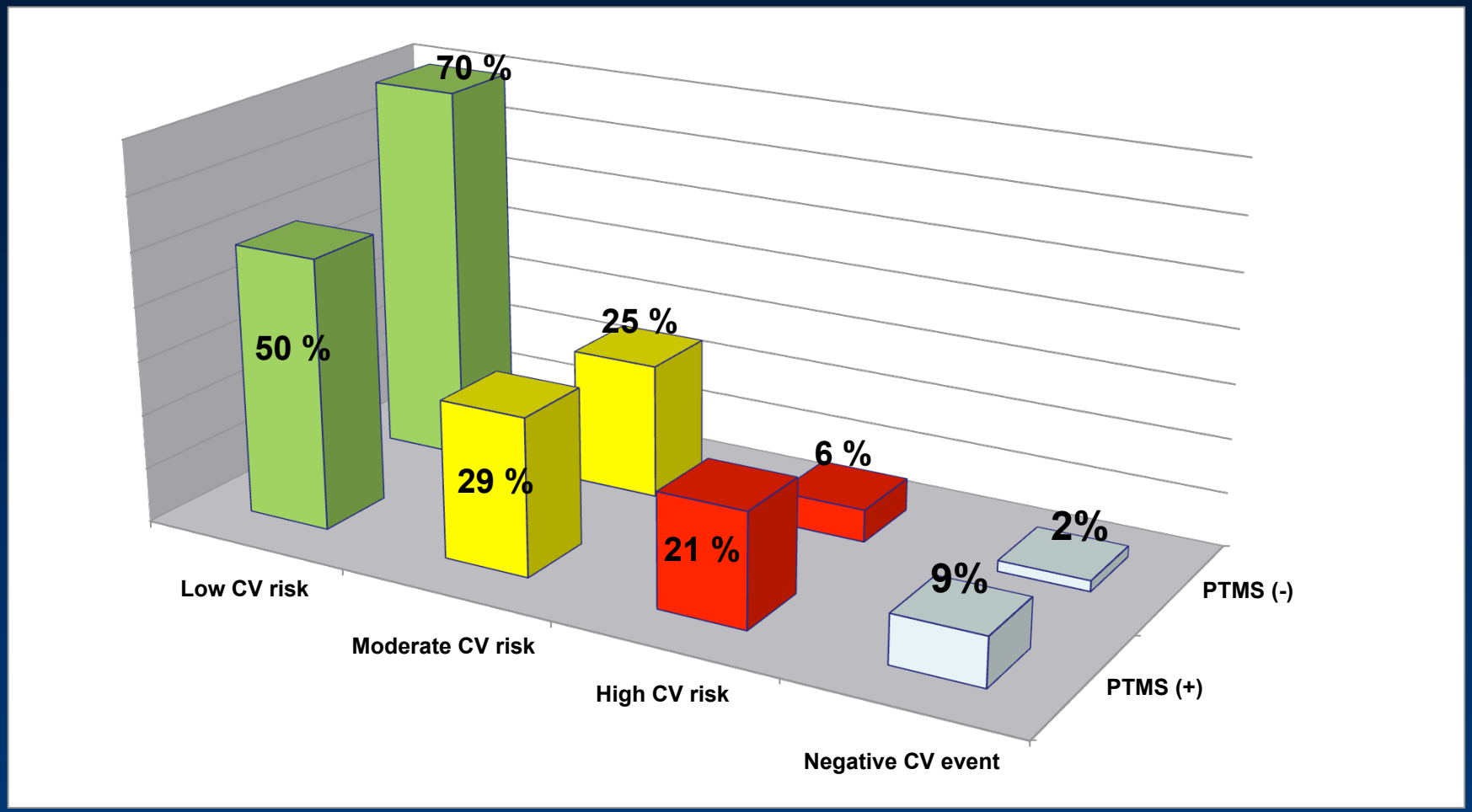
Narendra S. Choudhary Clin Transplant 2015

48 out of 156 liver transplant patients who developed PTMS : rate of appearance



Merli et al 2012

Cardiovascular risk in a population of 156 liver transplant patients according to the presence of PTMS



Merli et al 2012

Factors contributing to MS after liver transplantation

Factor	Metabolic consequences
Surgical	Denervation – increased insulin resistance (diabetes)
Steroid	Truncal fat distribution (obesity) ↑ Gluconeogenesis, ↓ glucose utilization (diabetes) ↓ β-cell insulin production Mineralocorticoid effect, ↑ SVR (hypertension)
Calcineurin inhibitor	Tac > CYA: β-cell toxicity, insulin secretion Induce insulin resistance (diabetes) CYA > Tac: Reduce cholesterol transport into bile and Bind/occupy LDL receptor (hyperlipidemia) Renal vasoconstriction (hypertension)
mTOR inhibitor	May increase insulin response (↓ diabetes) May block β-cell proliferation (↑ diabetes) ↑ Adipose tissue lipase activity, ↓ Lipoprotein lipase activity (hyperlipidemia)

Malnutrition in critically ill patients with cirrhosis

- Critically ill patients include those:
  - Hospitalized for severe complications of chronic liver disease
  - With acute-on-chronic liver failure
  - In an ICU
  - With acute alcoholic hepatitis

Recommendations	Grade of evidence	Grade of recommendation
Consider nutritional status and presence of sarcopenia. Provide nutritional support while treating other manifestations of severe decompensation	II-3 C	1
Daily energy intake should not be lower than 35–40 kcal/kg.BW/day, or 1.3x measured REE	II-2 B	1
Daily protein intake should not be lower than 1.2–1.3 g/kg.BW/day	II-2 B	1

Malnutrition in critically ill patients with cirrhosis

- Direct measurement of REE by indirect calorimetry is advisable
- As in all critically ill patients, tight glucose control is indicated
- Enteral or parenteral nutrition is more likely to be required

Recommendations	Grade of evidence	Grade of recommendation
Supplement dietary intake by enteral nutrition in patients unable to achieve adequate intake by mouth. If oral diet or enteral nutrition are not tolerated or contraindicated, provide parenteral nutrition	III A	1
Utilize standard nutrition regimens. Specialized regimens (e.g. BCAA-enriched, immune-enhancing diets) have not been shown to improve morbidity or mortality	II-1 B	2
In patients with HE, consider BCAA-enriched solutions	I A	1

EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

Malnutrition and other special considerations

Alcoholic liver disease and severe/acute alcoholic hepatitis

- Patients with active alcohol abuse may have a higher REE

Gastrointestinal bleeding

- Withhold enteral nutrition for 48–72 hours after acute bleeding due to risk of increased portal pressure and variceal re-bleeding

Recommendations	Grade of evidence	Grade of recommendation
Naso-gastroenteric tubes are not contraindicated in patients with non-bleeding oesophageal varices	II-2 A	1
Avoid PEG insertion in patients with cirrhosis due to risk of bleeding	III B	2
In cirrhosis and severe/acute alcoholic hepatitis, provide nutritional support as it may accelerate resolution of hepatic encephalopathy and improve survival in patients with low calorie intake	II-1 A	1

EASL CPG nutrtition in chronic liver disease. J Hepatol 2018; doi: 10.1016/j.jhep.2018.06.024

THE FUTURE FOR NUTRITION IN CHRONIC LIVER DISEASE

New research should address the following topics

- Nutritional strategies:
  - How should we evaluate sarcopenia (cut offs and normal values)?
  - Does the improvement in muscle mass and/or muscle function improve clinical outcomes?
  - Do ammonia-lowering strategies in decompensated cirrhosis reverse muscle loss and improve clinical outcomes?
  - Does a gradual increase in physical activity delay or reverse muscle loss and contractile dysfunction? What type and duration of exercise is beneficial in patients with cirrhosis?

EXERCISE IN CIRRHOSIS

Macias–Rodriguez 2016[42], RCT, 14 weeks	MELD 7–14, CP-A 64% n = 22, "Cardiopulmonary disease"	*Int:* Supervised exercise + 30% calories on exercise days (n = 11). *Ctrl:* (n = 11) All received nutrition therapy according to HBE	Between group comparison, with *Int* better than *Ctrl* for: HVPG being 6.5 mmHg lower ($p = 0.009$); within group comparison relative to baseline showed *Int* had significant improvements in ventilatory efficiency ($p = 0.033$). *Ctrl:* NSD
Roman 2016[64], RCT, 12 weeks	MELD 8 ± 0.4, CP-A 5.4 ± 0.2 n = 23, "Contraindication to exercise"	*Int:* supervised exercise (n = 14). *Ctrl:* relaxation programme (n = 9)	Within group comparison relative to baseline showed *Int* had: Muscle mass increase ($p < 0.01$); fat body mass decrease ($p = 0.003$); lean body mass increase ($p \leq 0.03$); fall risk decrease ($p = 0.02$) *Ctrl:* NSD
Kruger 2018[44], RCT, 8 weeks	CP-A 70% (n = 40), history of LVEF <60% or CAD, or positive outcome on exercise stress test	*Int:* home-based exercise + 250–350 kcal on exercise days (n = 20). *Ctrl:* usual care (n = 20) All pts received guideline-based nutrition counselling	Between group comparison, with *Int* better than *Ctrl* for: 6MWT increase by 33.7 m ($p = 0.02$). Between group comparison for *Int adherents* (≥80% training sessions) better than *Ctrls* for: 6MWT increase by 46.4 m ($p = 0.009$); peak VO_2 increase by 2.8 ml/kg/min ($p = 0.02$) [Study dropouts, n = 3]
Hiraoka, 2017[45], cohort, 12 weeks	CP-A 91% (n = 33), patients with "other organ disease" – CHF, chronic respiratory disease	Home-based exercise + 210 kcal snack and 13.5 g BCAA at night (n = 33)	Increases seen relative to baseline measures: Average daily steps ($p = 0.02$); muscle volume, leg and handgrip strength ($p < 0.01$ for each); BCAA/tyrosine ratio ($p = 0.001$) [Study dropouts, n = 2]

PRE SCREENING IS REQUIRED TO ESTABLISH EXERCISE SAFETY AND INTENSITY

Cirrhosis-related screening
(MELD >20, High-risk varices, hepatic encephalopathy, ascites, hepaic ence-Phalopathy, platelets, diabetes, diuretic therapy)

Cariopulmonary safety

Overall physiological competence

J Hep Apr 2018

EXERCISE TRAINING PRINCIPLES

“Start low, progress slowly, and be alert for symptoms”

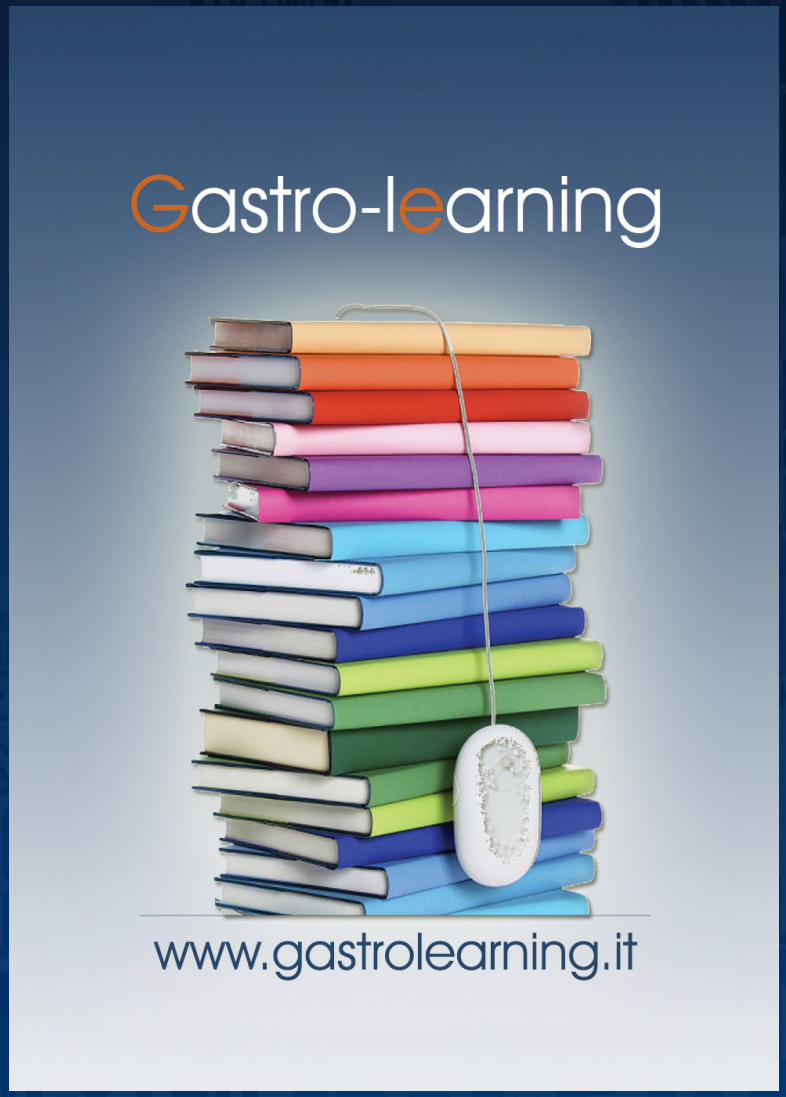
Encourage patients to take advantage of opportunities of Physical activity with-in the day-to-day routine.

Exercise is differentiated from physical activity as it is planned and performed on a repeated basis over an extended period of time for the purpose of improving fitness, Performance and health.

J Hep April 2018

New research should address the following topics

- Nutritional strategies:
  - Is the addition of supplements (leucine, isoleucine, or other nutrient supplements) needed to lower ammonia and increase mitochondrial intermediates during training?
  - How to implement therapies targeting muscle protein synthesis pathways or dysregulated muscle autophagy
  - How to overcome anabolic resistance or reverse the underlying causes of anabolic resistance in patients with cirrhosis



Grazie per l'attenzione

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