SAPIENZA
UNIVERSITÀ DI ROMA

Dottorato di Ricerca in Epato-gastroenterologia sperimentale e clinica, XXXVIII ciclo

Curriculum Gastroenterologia - codice SSD MEDS-10/A

Coordinatore Prof. Guido Carpino

"Body Composition in Liver Cirrhosis and After Transjugular Intrahepatic Portosystemic Shunt: Prognostic Impact and Clinical Assessment"

Tutor
Prof.ssa Manuela Merli

Dottorando
Dott. Simone Di Cola

INDICE

CHAPTER 1: NUTRITIONAL CHANGES IN PATIENTS WITH LIVER CIRRHOSIS

1.1 THE BURDEN OF MALNUTRITION IN GLOBAL HEALTH

Nutrition represents a fundamental determinant in the prevention, progression, and management of systemic and chronic diseases. In recent decades, increasing life expectancy, broader economic access, and the advent of novel therapeutic strategies for life-threatening conditions have substantially reshaped the clinical landscape of chronic disease management. In this context, malnutrition has emerged as a critical factor influencing morbidity and mortality, attracting growing attention in scientific research and fostering the development of precise clinical tools for its assessment, monitoring, and intervention[1]. Both undernutrition and overnutrition exert deleterious effects on health across the lifespan, underscoring the necessity for comprehensive nutrition and public health policies that address these conditions in alignment with Sustainable Development Goal Target 2.2, which aims to eliminate "all forms of malnutrition" (https://www.un.org/sustainabledevelopment/hunger/)[2]

Malnutrition is broadly defined as a state of imbalance between an individual's nutrient and energy intake and the body's physiological requirements to maintain growth, functional integrity, and overall health. This condition encompasses both undernutrition—including underweight, micronutrient deficiencies, wasting, and stunting—and overnutrition, such as overweight, obesity, and diet-related non-communicable diseases[3]. The consequences of malnutrition are multifaceted: beyond the direct impact of nutrient deficiencies, malnutrition exerts systemic effects that compromise the function of multiple organs and physiological systems, thereby increasing susceptibility to disease progression and adverse clinical outcomes, irrespective of disease severity or stage.

Among the most clinically significant manifestations of malnutrition are changes in body composition, particularly affecting skeletal muscle and adipose tissue. Sarcopenia, defined as the progressive loss of muscle mass, strength, and function, is considered a hallmark of malnutrition, with substantial implications for physical performance, clinical outcomes, and quality of life[4,5]. **Sarcopenia** is largely age-related, represents a para-physiological process of aging and its impact in older adults is well documented. Notably, in the context of various chronic and systemic

diseases, sarcopenia may develop prematurely. Indeed, global prevalence estimates indicate that sarcopenia affects between 8% and 36% of individuals under 60 years of age, and between 10% and 27% of those aged 60 years and older[6]. Sarcopenia is a condition that affects muscle function, resulting in impaired movement, physical independence, and daily activities. This can lead to isolation and reduced social interaction, ultimately impacting quality of life[7]. A more global way to explore how malnutrition and chronic disease affect patients' vulnerability to external inputs is to determine if they are frail. **Frailty** is a complex, age-related clinical condition involving multiple contributing factors that raises the risk of adverse outcomes in older people[8]. Frailty, like sarcopenia, can also affect younger people with advanced chronic diseases, impacting morbidity and mortality[9].

Aging not only reduces the skeletal muscle mass but also compromises overall muscle quality. Skeletal muscle is organized hierarchically, consisting of intramyocellular myofibrils, muscle fibers, and fascicles, all of which are enveloped by progressively thicker connective tissue layers: the endomysium, perimysium, and epimysium. With advancing age, obesity, chronic inflammation, and the presence of metabolic diseases, there is a progressive increase in ectopic fat deposition within skeletal muscle, a phenomenon referred to as **myosteatosis**[10].

Skeletal muscle adiposity can be broadly classified into three distinct compartments: (a) intermuscular adipose tissue (IMAT), which represents extracellular adipose tissue located beneath the fascia and between muscle groups; (b) intramuscular adipose tissue, which refers to extracellular adipose tissue embedded within an individual muscle; and (c) intramyocellular lipids (IMCL), which are lipid droplets stored within muscle fibers themselves[11,12].

Skeletal muscle mass is a main determinant of insulin sensitivity. However, various extracellular stressors—including nutrient overload, hyperinsulinemia, glucocorticoid exposure, and systemic inflammation—can elicit intracellular stress responses in metabolic tissues such as muscle and adipose tissue[13]. These perturbations impair insulin signaling and hinder its ability to regulate glucose and lipid metabolism effectively. Importantly, myosteatosis has been consistently associated with aging, obesity, visceral adiposity, and an elevated risk of type 2 diabetes mellitus (T2DM)[14].

Beyond its metabolic consequences, fat infiltration within skeletal muscle also contributes to a state of chronic, low-grade inflammation. This process is partly mediated by dysregulated secretion of adipokines (e.g., leptin and adiponectin) and pro-inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), both of which play central roles in adipose tissue homeostasis. In particular, IL-6 released from adipocytes—including those embedded within intermuscular adipose tissue (IMAT)—can trigger inflammatory signaling cascades, which are further amplified in the presence of TNF-α[15]. Sustained activation of these pathways fosters a chronic inflammatory milieu, suppresses anabolic signaling, and disrupts muscle protein turnover, thereby impairing muscle homeostasis—an effect commonly referred to as lipotoxicity[16]. Clinically, these alterations are linked to adverse disease trajectories across stages and are associated with reduced muscle stiffness and compromised contractile function[17,18]

A key mechanism underlying these changes involves fibro-adipogenic progenitors (FAPs). Under physiological conditions, FAPs undergo regulated apoptosis; however, in the context of chronic inflammation, they become pathologically activated and differentiate into myofibroblasts and adipocytes[19]. Dysregulated FAP activity leads to abnormal adipose infiltration within skeletal muscle and disruption of the extracellular matrix (ECM). This maladaptive remodeling increases fibrosis and fatty infiltration by disturbing fiber alignment and replacing contractile elements with non-functional tissue[19-21].

At last, adiposity has demonstrated a direct effect on prognosis by increasing death for all causes[22]. Visceral Adipose Tissue (VAT), represented by fat around abdominal viscera in mesentery and omentum, is different from Subcutaneous Adipose Tissue (SAT), accumulated in the space between abdominal wall and muscle plan. Adipocytes from VAT are more insulin-resistant than SAT adipocytes. Abdominal obesity increases levels of inflammatory markers, like TNF-a, CRP and IL-6. Infact, VAT is more infiltrated with inflammatory cells and is more capable of generating those proteins than SAT[23]. High Visceral to Subcutaneous Adipose Tissue (V/S) ratio is associated with clinical adverse events, particularly with higher risk of cardiovascular events[24], metabolic syndrome, Nonalcoholic Fatty Liver Disease and Liver Fibrosis[25,26], poor outcome in cancer population and in postoperative settings[26-28]. Lastly, several potential factors, such as blood flow, adipocyte size, lipid

content, and fluid-to-triglyceride ratio might impact the quality of the adipose tissue, especially of SAT[29,30]. Adipose quality can be indirectly measured with CT-scan by the evaluation of mean attenuation of Hounsfield Unit (HU) in the SAT at L3 slice[30]. Lower adipose tissue radiodensity (i.e. more negative CT radiodensity) has been linked to the larger lipid droplets within hypertrophic adipocytes. Adipose tissue radiodensity is a more robust predictor of insulin resistance than adipose tissue volume in obese and overweight individuals[31]. Higher SAT radiodensity might represent adipose tissue fibrosis. Having higher SAT radiodensity was associated with shorter survival in patients with multiple myeloma[32].

At last, adiposity itself has been shown to exert a direct negative influence on prognosis, being associated with increased all-cause mortality[33]. Visceral adipose tissue (VAT), which accumulates around the abdominal viscera within the mesentery and omentum, is metabolically distinct from subcutaneous adipose tissue (SAT), located between the abdominal wall and the muscle fascia. VAT adipocytes are typically more insulin-resistant than their SAT counterparts, and abdominal obesity is strongly linked to higher circulating concentrations of inflammatory mediators, including TNF-α, C-reactive protein (CRP), and IL-6. Indeed, VAT is more heavily infiltrated by immune cells and demonstrates a greater capacity to produce pro-inflammatory proteins compared to SAT[34].

A higher visceral-to-subcutaneous adipose tissue (V/S) ratio has emerged as a clinically relevant biomarker, being consistently associated with adverse outcomes. Specifically, increased V/S ratio correlates with elevated cardiovascular risk[35], a higher prevalence of metabolic syndrome, and progression of nonalcoholic fatty liver disease (NAFLD) and liver fibrosis. Moreover, excess visceral adiposity has been linked to poor prognosis in oncologic populations and to unfavorable postoperative outcomes[25,26,28].

Beyond the quantity of adipose depots, several structural and functional characteristics influence adipose tissue quality. Factors such as regional blood flow, adipocyte size, intracellular lipid content, and the fluid-to-triglyceride ratio may determine the biological properties of SAT and VAT[29,30]. Imaging-based approaches, particularly CT scanning, allow indirect assessment of these features through radiodensity analysis. Measurement of mean attenuation values in SAT at the L3 vertebral level provides insights into tissue composition[30]. Lower CT radiodensity

(i.e., more negative HU) reflects the presence of enlarged lipid droplets within hypertrophic adipocytes, and has been shown to predict insulin resistance more robustly than adipose volume alone[31]. Conversely, higher SAT radiodensity has been proposed as a marker of adipose tissue fibrosis, a maladaptive remodeling phenomenon, and has been associated with reduced survival in patients with multiple myeloma[32].

In conclusion, it's emerging that deep evaluation of quantitative and qualitative changes in muscle mass and adipose tissue is essential to better understand the pathophysiology of chronic and metabolic diseases and to better stratify the risk of adverse events. Both the distribution and the intrinsic quality of adipose tissue represent critical determinants of metabolic and clinical outcomes.

1.2 NUTRITIONAL CHANGES IN CIRRHOSIS

Cirrhosis is a chronic, pro-inflammatory condition that represents the terminal stage of diverse chronic liver diseases. It is characterized by impaired hepatic synthetic capacity and profound vascular alterations that ultimately result in portal hypertension (PH)[36]. As the largest and most metabolically complex organ in the human body, the liver plays a central role in nutrient metabolism; consequently, malnutrition is highly prevalent among individuals with cirrhosis. Reported prevalence rates vary widely, ranging from 5% to 99%, depending on the characteristics of the study population and the diagnostic criteria applied[37-40]. The etiology of malnutrition in cirrhosis is multifactorial. Contributing mechanisms include inadequate dietary intake, impaired nutrient absorption, and profound alterations in substrate metabolism secondary to liver dysfunction[41]. Furthermore, both acute and chronic complications of cirrhosis may restrict oral intake[42] and/or increase energy expenditure.

Importantly, malnutrition in this context has significant prognostic implications. It is strongly associated with increased mortality, higher incidence of portal hypertension–related complications, greater susceptibility to infections, and prolonged hospital stays[43-46].

Sarcopenia represents the most extensively investigated muscle alteration in patients with cirrhosis. Since the 1970s, malnutrition has been increasingly recognized as a major concern in this population[47,48]. Over the past decade, interest in this topic has grown substantially. A PubMed© search for the terms “sarcopenia” AND “cirrhosis” retrieved only 21 publications in 2013, compared with 241 in 2023, underscoring the expanding scientific focus.

A recent meta-analysis including 8,945 patients across 40 studies reported an overall prevalence of sarcopenia of 41% (95% confidence interval (95%CI, 34–48%), with significantly higher risk observed in male patients and in those with HE[49]. The prevalence of sarcopenia is also closely related to the severity of liver disease, being substantially higher in patients with Child-Pugh class B–C compared with those classified as Child-Pugh (CP) class; according to the meta-analysis conducted by Mazeaud et al., the mean prevalence of sarcopenia in patients with cirrhosis is estimated at 33%. (95%CI 0.31–0.35), 36% (95%CI 0.34–0.39), and 46% (95%CI 0.43–0.50) in CP-A, CP-B, and CP-C groups, respectively [50]. Similarly, prevalence of sarcopenia is approximately 40% in patients awaiting liver transplantation (LT)[51]. Overnutrition may also contribute to muscle loss, primarily through the effects of an unhealthy lifestyle, lipotoxicity, and the induction of a chronic pro-inflammatory state[52]; the coexistence of sarcopenia and obesity is known as sarcopenic obesity, with a reported prevalence of 20-35%[53]. Sarcopenia significantly influences the clinical course of patients with cirrhosis. With regard to survival, it has been identified as a major prognostic determinant, particularly in individuals with decompensated disease. A recent comprehensive meta-analysis by Tantai et al. demonstrated that the presence of sarcopenia is associated with a twofold increase in mortality risk. Specifically, the probability of 1-year survival was 76.6% in patients with sarcopenia, compared to 93.4% in those without[54]. Sarcopenia also affects post-LT survival[55] with a relative risk of 1.75 (95% CI: 1.49-2.06)[56]. Zhou et al. reported that patients undergoing LT with concomitant sarcopenia experienced significantly worse postoperative outcomes compared to those without sarcopenia. Specifically, sarcopenic patients had longer intensive care unit stays (4.1 ± 2.2 vs. 3.1 ± 1.1 days, $P = 0.008$), a higher incidence of major complications (45.2% vs. 22.1%, $P = 0.001$), and greater postoperative mortality (15.1% vs. 2.9%, $P = 0.003$)[57]. Beyond transplant settings, sarcopenia has been consistently associated with an increased risk of adverse clinical events in cirrhosis, including more frequent

episodes of decompensation and hospitalization, particularly those related to overt[57-59] and minimal HE[60-64]. Furthermore, sarcopenia has been identified as a risk factor for the development of acute-on-chronic liver failure (ACLF)[65] and is linked to increased susceptibility to infections[66]. These profound alterations in the clinical course ultimately exert a detrimental impact on the quality of life of patients with cirrhosis who develop sarcopenia[67]. Considering its relevance in the prognostic assessment, we have previously proposed to include the diagnosis of sarcopenia, myosteatosis and HE in the model for end-stage liver disease (MELD) and, as a result, the MELD-Sarco-Myo-HE score added accuracy to the MELD score alone for 6- and 3-months mortality[68].

Frailty in the elderly has been extensively investigated and represents a broader clinical syndrome than muscle loss alone, although it is closely related to sarcopenia[69]. In patients with cirrhosis, frailty has been consistently associated with increased waitlist mortality, independent of traditional clinical events and prognostic scores[70]. To address this, a disease-specific assessment tool, the Liver Frailty Index (LFI), has been proposed and validated, particularly in individuals with decompensated cirrhosis[70] and those awaiting liver transplantation[71-73]. Importantly, longitudinal changes in LFI scores have been shown to predict mortality and delisting from the transplant waitlist, independent of baseline frailty status and MELD-Na values[74]

Muscle quality impairment has recently emerged as a relevant prognostic factor in patients with cirrhosis. Myosteatosis appears to be strongly linked to adverse outcomes. Driven by the systemic pro-inflammatory milieu characteristic of cirrhosis, myosteatosis has been shown to increase mortality risk independently of the severity of liver disease. Its overall prevalence in cirrhosis is estimated at approximately 45%; however, higher rates are observed among women, patients with BMI, those with a metabolic etiology of liver disease, and those with more advanced stages of cirrhosis[75]. Montano-Loza *et al.* demonstrated in a retrospective cohort that both sarcopenia [hazard ratio (HR) 2.00, 95% confidence interval (CI) 1.44–2.77, $P < 0.001$] and myosteatosis (HR 1.42, 95% CI 1.02–1.07, $P = 0.04$) are independently associated with mortality in patients evaluated for liver transplantation[76]. These findings have been corroborated by subsequent studies, and a recent meta-analysis confirmed the association between myosteatosis and adverse survival outcomes,

despite limitations related to data quality and heterogeneity across studies[77]. The authors of the meta-analysis concluded that one of the major limitations in evaluating studies on the role of myosteatosis in cirrhosis is the lack of universally accepted cut-offs specifically validated for liver diseases through prospective high-quality studies. With this aim, we have developed a study protocol to define and validate new cut-offs for the diagnosis of myosteatosis in cirrhosis[78]. Beyond its impact on survival, myosteatosis has also been linked to several clinically relevant complications. Patients with myosteatosis exhibit a higher risk of HE[57,64], longer hospital stays[79], impaired muscle function, and an increased risk of frailty[80,81]. Myosteatosis may represent an early or prodromal stage in the trajectory toward overt muscle loss and sarcopenia. Supporting this hypothesis, Geladari *et al.* found that myosteatosis is more frequently detected in younger patients and in earlier stages of cirrhosis[82]. Furthermore, they demonstrated that muscle attenuation, measured in HU as a radiological marker of fat infiltration, progressively decreases in parallel with declining muscle function and the transition from isolated myosteatosis to combined muscle loss. A plausible mechanistic explanation lies in the concept of lipotoxicity: the accumulation of ectopic fat within muscle fibers may impair muscle metabolism, promote oxidative stress, and trigger inflammatory pathways, thereby accelerating functional decline and contributing to the adverse prognosis observed in cirrhosis.

Beyond muscle quantitative and qualitative alterations, modifications in adiposity can also contribute to impact morbidity and mortality in cirrhosis. Different adipose tissue compartments appear to exert distinct prognostic effects. High visceral adiposity has been shown to negatively influence survival in patients with HCC and esophageal varices[83] and survival after LT[84]; moreover, VAT seems to increase the risk of HCC development and recurrence in male patients with cirrhosis[85]. Conversely, low subcutaneous adiposity has emerged as an independent predictor of mortality in female patients with cirrhosis[86]. In this subgroup, alcohol-related liver disease was the most common etiology, and reduced SATI correlated with both hepatic venous pressure gradient and the presence of decompensation[87]. Beyond the quantity of adipose tissue, qualitative aspects are also clinically relevant: high visceral and subcutaneous adipose tissue radiodensity have both been associated independently with shorter survival, response to HCC treatments, portal hypertension degree, and an increased risk of liver decompensation[88,89]. A prospective cohort study

by Tapper E. B. et al., has evaluated 274 patients with cirrhosis using CT-derived Analytic Morphomics® to assess body composition. The findings demonstrate that both muscle quantity/quality and fat density are independent predictors of mortality and decompensation, outperforming MELD in prognostic accuracy, particularly in compensated cirrhosis[90]. SAT density emerged as the strongest predictor of first decompensation. This finding was further supported by Ebadi and colleagues in a large retrospective study, which demonstrated that high SAT radiodensity is common and is associated with increased mortality in patients with cirrhosis[91].

1.3 PHYSIOPHATOLOGY OF MALNUTRITION IN CIRRHOSIS

Malnutrition in cirrhosis could be related to the group of Disease-related malnutrition (DRM) which describes a nutrition- and inflammation-related disorder that results from prolonged acute or chronic disease and lack of nutrient intake or absorption leading to compromised body composition and function. The diagnosis is made by the combination of at least one of the phenotypical (unintentional loss of body weight, or reduced muscle mass) and etiological criteria[92]. The mechanisms of DRM and sarcopenia in cirrhosis are multifactorial and not fully understood. Reduced nutrient intake—driven by anorexia, dysgeusia, nausea, dietary restrictions, and frequent fasting[41]—combines with maldigestion and malabsorption due to cholestasis, drug-related diarrhea, pancreatic insufficiency[93], and small intestinal bacterial overgrowth[94]. These factors are compounded by systemic inflammation, endotoxemia, oxidative stress[95], hormonal disturbances (low testosterone, GH deficiency, altered ghrelin-leptin axis)[96,97], and hyperammonemia[98]. A pivotal role is played by altered macronutrient metabolism[99]: impaired glycogen storage and accelerated gluconeogenesis shift energy production from carbohydrates to fat oxidation, promoting proteolysis of skeletal muscle amino acids, particularly BCAAs, and ultimately impairing protein synthesis[41]. This metabolic imbalance, equivalent to prolonged starvation after a short fast, sustains muscle depletion and sarcopenia. Hypermetabolism—present in up to one-third of cirrhotic patients—further elevates resting energy expenditure through sympathetic nervous system overactivity and catecholamine excess, increasing nutrient demand and accelerating catabolism[100]. We have recently demonstrated that patients with cirrhosis are at high risk of energy and protein intake deficit, particularly in inpatients setting (91% Vs 73.9% for the energy intake respectively and 84% Vs 61% for the protein

intake) and in female[101]; moreover, the inpatient group had significantly lower BMI, mid-upper arm circumference, triceps skinfold and higher frailty compared to outpatients.

Focusing on sarcopenia, the pathogenesis is multifactorial and reflects profound disturbances in muscle protein homeostasis[102]. Contributing factors include hepatocellular necrosis with cytokine release, hyperammonaemia, endotoxemia, hormonal imbalances (low testosterone, altered GH/IGF-1 axis), ethanol toxicity, and systemic inflammation[69]. These perturbations lead to anabolic resistance, where nutrients and physical activity fail to stimulate protein synthesis, and activate catabolic pathways such as autophagy while impairing mTORC1 signaling. Hyperammonaemia, in particular, drives myostatin upregulation, mitochondrial and ribosomal dysfunction, altered amino acid metabolism, and glutamine–leucine exchange, thereby aggravating proteolysis[103,104]. In a previous comprehensive review, we have summarized the central role of hyperammonemia in its relationship with the sarcopenia: impaired hepatic clearance and portosystemic shunting lead to systemic accumulation of ammonia, which directly impairs protein synthesis (via mTORC1 inhibition, GCN2 activation, and impaired translation), alters the TCA cycle and mitochondrial function, and induces oxidative stress with contractile dysfunction. Muscle acts as an auxiliary ammonia buffer through glutamine synthetase, but sarcopenia reduces this capacity, further predisposing to HE. Hyperammonemia also increases myostatin expression and autophagy, amplifying muscle loss[58]. Endotoxemia and pro-inflammatory cytokines (IL-6, TNF-α) further suppress protein synthesis through NF-κB activation and ubiquitin-proteasome signaling. Additionally, systemic hypermetabolism and the “accelerated starvation” state of cirrhosis increase reliance on fat oxidation and amino acid catabolism, worsening muscle loss. Altogether, these mechanisms converge to create a sustained imbalance favoring proteolysis over protein synthesis, ultimately leading to progressive sarcopenia and frailty in cirrhosis.

In case of sarcopenic obesity, the pathophysiology became more complex, with the coexistence of excess adiposity and muscle loss, driven by chronic low-grade inflammation, insulin resistance, oxidative stress, and endocrine changes. Expansion of white adipose tissue and intramuscular lipid infiltration promote proinflammatory cytokine release, lipotoxicity, mitochondrial dysfunction, and impaired proteostasis,

leading to reduced protein synthesis and increased catabolism. Central mechanisms involve dysregulated mTORC1 and FoxO signaling, hormonal decline (testosterone, GH, estrogen), and myokine alterations. This adipose–muscle crosstalk establishes a vicious cycle that not only accelerates sarcopenia but also increases the risk of metabolic disorders, cardiovascular disease, frailty, and mortality[52]

Studies focused on the histological process of muscle loss are lacking in cirrhosis. Recently, Motamedrad et al. demonstrated that patients with decompensated cirrhosis present a distinctive myopathy characterized by selective atrophy of type II muscle fibres (which are primarily responsible for generating strength and power) and abnormal nuclear positioning within myofibres (a sign of cellular distress)[105]. Using rectus abdominis biopsies collected during LT, the study revealed that fibre type II cross-sectional area was significantly reduced, while the proportion of centralized nuclei was markedly increased compared to compensated patients. Notably, muscle triglyceride content was lower in decompensated cirrhosis, suggesting a distinct pathophysiological profile compared to other chronic conditions where myosteatosis is prevalent. These findings indicate that muscle impairment in advanced cirrhosis is not only quantitative, as reflected by reduced muscle mass, but also qualitative, involving structural and functional abnormalities at the cellular level.

As a result, myosteatosis reflects muscle-type-specific and sex-dependent metabolic adaptations to lipid overload[106]. Oxidative fibers preferentially oxidize fatty acids, whereas glycolytic fibers tend to re-esterify them into triglycerides, highlighting distinct vulnerability to lipotoxicity[107]. Excessive intramuscular fat deposition alters fiber orientation, promotes inflammation, and reduces strength, with early adaptations involving fiber transition from type II to type I[108,109]. In cirrhosis, mechanisms such as hyperammonemia[110,111], insulin resistance[112], mitochondrial dysfunction[113], and impaired adipose tissue lipid storage[114] have been implicated, but direct evidence remains limited. Experimental studies demonstrate that myosteatosis impairs mitochondrial oxidative phosphorylation, reduces ATP synthesis[113], and interferes with protein metabolism, potentially leading to muscle atrophy. However, most available data derive from diet-induced obesity or in vitro models, underscoring the need for cirrhosis-specific mechanistic studies.

In the context of metabolic syndrome, obesity, diabetes, and steatotic liver diseases, the underlying pathophysiological pathways have become increasingly complex and

tightly interconnected. A recent review has summarized this relationship[15]: Metabolic dysfunction–associated steatotic liver disease (MASLD) is tightly linked to skeletal muscle dysfunction, where insulin resistance, myosteatosis, and sarcopenia act as key drivers of disease progression. At the molecular level, impaired skeletal muscle glucose disposal promotes hyperglycemia and hyperinsulinemia, which enhance hepatic de novo lipogenesis and perpetuate steatosis. Lipotoxicity from elevated nonesterified fatty acids disrupts insulin signaling through PKC activation, reduced IRS-1/Akt pathways, and toll-like receptor–mediated inflammation. In parallel, systemic inflammation and adipose-derived signals further impair muscle insulin sensitivity, while alterations in myokine profiles, such as reduced irisin and elevated myostatin, exacerbate both muscle catabolism and hepatic injury. Conversely, hepatokines including fetuin-A, LECT2, and FREP1 promote skeletal muscle insulin resistance and metabolic dysfunction, creating a vicious bidirectional cycle. Myosteatosis contributes through intramuscular adipose tissue–driven inflammatory and lipotoxic effects, whereas sarcopenia reflects chronic imbalance between anabolic and catabolic signals, aggravated by immobility, oxidative stress, and dysregulated organokine signaling.

Adipose tissue functions as an active endocrine organ, modulating systemic metabolism via secretion of adipokines such as adiponectin, leptin, TNF-α, and IL-6[116]. Visceral adipose depots exhibit increased lipolytic activity and a pro-inflammatory stromal milieu, leading to elevated free fatty acid uptake[117] , activation of NF-κB pathways, and impaired insulin signaling through IRS/PI3K-Akt dysregulation. Deep subcutaneous fat is characterized by higher saturated fatty acid content, which paradoxically associates with preserved insulin sensitivity, suggesting depot-specific lipidomic signatures. In the liver, triglyceride accumulation drives MAFLD, progressing to NASH via oxidative stress, mitochondrial dysfunction, ER stress, and activation of stellate cells promoting fibrogenesis through TGF-β and collagen deposition[118]. Crosstalk between adipose tissue and the liver amplifies these mechanisms, with altered adipokine secretion and ectopic lipid deposition exacerbating systemic insulin resistance.

In summary, the pathophysiology of nutritional alterations in cirrhosis is highly complex, with the different components of malnutrition being closely interconnected.

Future research should move beyond examining individual aspects of malnutrition focusing the interplay between multiple pathophysiological pathways.

1.4 DIAGNOSIS AND THERAPEUTIC APPROACH TO MALNUTRITION IN CIRRHOSIS

The latest European Association for the Study of the Liver (EASL) guidelines on nutrition in cirrhosis recommend systematic screening of all patients with advanced chronic liver disease, particularly when decompensated, due to the prognostic impact of malnutrition[119]. In real-world practice, however, nutritional screening in patients with cirrhosis remains underutilized, and there is still no universally accepted tool. Among the available options, the Royal Free Hospital–Nutritional Prioritizing Tool (RFH-NPT) is rapid to apply and has been shown to correlate with prognosis in cirrhosis[120]. Other tools, such as NRS-2002[121] and MUST[122], are validated in hospitalized patients but not specifically for liver disease. In direct comparisons, RFH-NPT demonstrated greater sensitivity than NRS-2002 in detecting malnutrition risk in patients with cirrhosis[120]. Pending the next update of the ESPEN guidelines, the most recent version (2020) concludes that no tool has yet been rigorously validated in cirrhosis, although the RFH-NPT currently represents the most suitable option[123].

Sarcopenia is defined as a generalized loss of muscle mass, strength, and function. As a consequence, its diagnosis can rely on both functional tests and quantitative imaging techniques. The current gold standard is the assessment of muscle mass by CT or MRI at the L3 vertebral level, where the skeletal muscle area is normalized for height to calculate the skeletal muscle index (SMI)[119]. For patients with cirrhosis, validated cut-off values are 50 cm^2/m^2 in men and 39 cm^2/m^2 in women, with low muscle mass being independently associated with poor clinical outcomes[124]. Despite their accuracy, the routine use of CT and MRI is limited by cost, radiation exposure, and availability, and current guidelines discourage their use when the sole indication is nutritional assessment. Consequently, clinicians often rely on alternative methods such as anthropometry (e.g., mid-arm muscle circumference, triceps skinfold thickness), DEXA, and BIA. However, these approaches present limitations, particularly regarding hydration status and measurement specificity[41]. Among functional measures, handgrip strength is a simple, non-invasive, and reliable predictor of both complications and survival[125]. Time-Up-and-Go (TUG) test is a rapid tool used to evaluate mobility, balance, walking ability, and risk of falls,

indirectly reflecting muscle strength and function[126]. In the context of limitations in the practical approach of detecting sarcopenia by gold-standard techniques, researchers have explored the role of ultrasound in the mass mass measurement. Ultrasound (US) emerges as a promising, non-invasive, bedside tool, with validated parameters such as muscle thickness, cross-sectional area, pennation angle, fascicle length, and echo-intensity. Studies in cirrhosis show strong correlations between US measures and reference standards (CT, DXA, handgrip strength), with some evidence linking US-derived metrics to outcomes like survival and hospitalization[127]. Despite methodological heterogeneity and technical limitations (probe pressure, ascites, obesity), US provides a feasible and reproducible method for muscle assessment[128]. Very recently, Piano S et al., have found in a prospective study that the rectus femoris cross-sectional area is accurate and associated with clinical events and mortality in decompensated cirrhosis[129]. Actually, there is not enough strong data to validate ultrasound (US) as a gold-standard technique in cirrhosis for diagnosing sarcopenia. In this context, we are working on a meta-analysis to collect all available data for a more generalized conclusion (we have registered it on PROSPERO - ID CRD420251056162). At the same time, we are building a multicenter prospective study to validate the US in predicting mortality and further decompensation in patients with cirrhosis and first decompensation. The relative study protocol is under evaluation for the publication on BMJ Open.

In clinical practice, the most pragmatic strategy is to adopt a multimodal assessment, combining imaging when available with anthropometric measurements and functional testing, in order to achieve a comprehensive evaluation of sarcopenia.

Frailty has recently been investigated in several studies with the aim of identifying a specific assessment tool for patients with liver cirrhosis. The combination of sex with the results of functional and strength tests (TUG test, balance test, and handgrip strength) allows stratification of patients into robust, pre-frail, and frail categories, each with distinct prognostic implications in cirrhosis[73], and particularly among candidates awaiting LT[74].

Myosteatosis, defined as fat infiltration within skeletal muscle, is typically detected using cross-sectional imaging modalities such as CT or MRI. On CT, adipose tissue is characterized by low radiodensity, expressed in Hounsfield Units (HU). Consequently, fat infiltration into skeletal muscle reduces mean muscle attenuation

values, which can be quantified at the level of the third lumbar vertebra (L3)[106]. Measurement of mean muscle attenuation in HU at the L3 level on CT scans is currently considered the gold standard for the diagnosis and quantification of myosteatosis. MRI, however, offers superior sensitivity and specificity for the quantification of intramuscular fat, particularly in the setting of cirrhosis where fluid retention can interfere with CT-based attenuation values[130]. Quantitative MRI techniques, such as proton density fat fraction (PDFF) analysis on T1-weighted sequences, directly measure fat content by suppressing the water signal and expressing fat infiltration as a percentage[131]. Despite these advantages, the high cost and limited availability of MRI make CT the most widely used modality for diagnosing myosteatosis. The diagnostic cut-offs for myosteatosis on CT are currently based on body mass index (BMI), reflecting the association between fat infiltration and obesity. Specifically, mean muscle attenuation values <41 HU in patients with BMI <25 and <33 HU in those with BMI ≥25 are used as diagnostic thresholds[132]. These cut-offs, however, were derived from oncological cohorts and have not been validated in patients with cirrhosis. This raises concerns regarding their applicability, particularly given the limited accuracy of BMI in patients with cirrhosis due to ascites and fluid overload[133]. In this regard, Ebadi et al. (2022) proposed sex-specific cut-offs for patients with cirrhosis listed for LT: <33 HU for males and <28 HU for females[134]. Although these findings are promising, they have not yet been validated, and their generalizability remains uncertain.

Adiposity can be reliably assessed by CT scan sequences. As described above, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) can be clearly distinguished at the L3 vertebral level on both CT and MRI. The commonly applied HU thresholds are −190 to −30 HU for SAT[135] and −150 to −50 HU for VAT[136]. Continuous variables of SAT and VAT have frequently been evaluated for their prognostic value in various diseases, including cirrhosis, with SAT generally showing a positive association and VAT a negative one. However, validated cut-offs for defining pathological high VAT or low SAT values are lacking, particularly in cirrhosis.

In this context, Zhu et al.[137] retrospectively identified adiposity cut-off values associated with mortality in patients with cirrhosis. Specifically, SAT index (SATI) thresholds of 19.7 and 51.8 cm^2/m^2 were established, classifying SATI as low (<19.7

cm²/m²), moderate (19.7–51.8 cm²/m²), or high (>51.8 cm²/m²). Similarly, VAT index (VATI) cut-offs of 9.8 and 40.2 cm²/m² were proposed, corresponding to low (<9.8 cm²/m²), moderate (9.8–40.2 cm²/m²), and high (>40.2 cm²/m²) categories, with hazard ratios remaining below 1.2 at these thresholds.

Beyond quantity, the radiodensity of SAT has recently emerged as a novel parameter reflecting tissue quality. SAT radiodensity has been suggested as an indirect marker of inflammation and atrophy within adipose tissue, and lower values have been shown to inversely correlate with prognosis[91]. High SAT radiodensity in cirrhosis was defined as >-83 HU in females and >-74 HU in males.

Therapeutic approaches for nutritional impairment in cirrhosis are limited and mainly focused on muscle loss.

Current standard recommendations emphasize adequate dietary protein intake, energy provision, and moderate physical activity[123]; however, these non‑pharmacological strategies often provide only partial benefit. We have recently summarized current and future therapies for sarcopenia in cirrhosis[140]. Among pharmacological agents, several show promise: branched‑chain amino acids (BCAAs) have some evidence for improving muscle mass/function; ammonia‑lowering agents such as LOLA, and drugs like L-carnitine. Testosterone and IGF-1 therapies are mentioned, though concerns remain (e.g. side effects, long-term safety) and data are limited. We have demonstrated in a RCT the additional role of Beta-Hydroxy-Beta-Methylbutyrate (HMB) supplementation in the improving of muscle function (chair stand test: 14.2 ± 5 s vs. 11.7 ± 2.6 s, $p < 0.05$; six-minute walk test: 361.8 ± 68 m vs. 409.4 ± 58 m, $p < 0.05$) and muscle mass (quadriceps muscle mass measured by ultrasound - 4.9 ± 1.8 vs. 5.4 ± 1.8 mm, $p < 0.05$) and frailty (LFI 4.1 ± 0.4 vs. 3.7 ± 0.4, $p < 0.05$)[139]. Other emerging/experimental agents included myostatin/follistatin modulation, terlipressin, and interventions to target inflammation and metabolic dysregulation. An interesting drug recently studied was an androgen receptor agonist, LPCN 1148, demonstrating effect in muscle gain and reduction in HE incidence[140]. Key gaps identified include small sample sizes, heterogeneity of study designs, lack of randomized controlled trials with clinically meaningful endpoints, and scarce data stratified by sex or by cirrhosis severity. Moreover, many candidate drugs are emerging, robust evidence for widespread clinical application is still lacking; future research should aim to validate

promising agents in larger, well-designed trials to define efficacy, safety, and optimal patient selection.

1.6 THE ROLE OF NUTRITION IN THE SETTING OF TIPS

Nutrition is a key element in patients undergoing interventional therapies. The prognostic role of malnutrition after surgery is well established, as it increases the risk of post-surgical morbidity and mortality[123]. In cirrhosis, this aspect is even more relevant, given the intrinsic risk of decompensation after surgery in patients with portal hypertension and the central role of nutrition in the natural course of the disease[141]. Malnutrition and sarcopenia increase the risk of post-surgical decompensation, the need for Intensive Care Unit (ICU) admission, longer hospital stays, higher rate of infections and mortality, especially in the case of LT[55, 142-144].

Transjugular intrahepatic portosystemic shunt (TIPS) is a radiological intervention aimed at reducing portal hypertension by diverting portal blood flow directly into the suprahepatic venous system. The amelioration of portal hypertension leads to a reduction in liver-related complications and an overall improvement in prognosis[145]. On the other hand, TIPS placement is associated with a non-negligible rate of post-procedure complications, particularly HE, cardiac insufficiency, and liver failure. Recently, prediction of post-TIPS events has become a trending topic for improving patient selection. Older age, advanced liver disease (based on MELD or Child-Pugh scores), and a prior history of HE are well-recognized risk factors for post-TIPS HE and poor clinical outcomes[146].

Beyond these known risk factors, nutritional assessment has gained increasing relevance in recent years. The latest European guidelines on TIPS explicitly state that "*nutritional status is an important prognostic factor in patients with cirrhosis, and diagnosis of sarcopenia may prompt interventions to improve patient outcomes*"[146]. Despite these statements, evidence remains insufficient to mandate routine nutritional screening or the implementation of structured nutritional programs before TIPS placement. Conversely, British guidelines on TIPS clearly include nutrition as part of the screening process for patient selection, together with demographic, renal, cardiac, liver, anatomical, and vascular evaluation[147].

Baseline nutritional status influences the incidence of post-TIPS complications, similarly to what is observed in surgical settings. Li J. et al. explored the prognostic value of the Controlling Nutritional Status (CONUT) score in predicting post-TIPS HE[148]. The CONUT score, which is based on baseline serum albumin, total cholesterol, and total lymphocyte count, was originally developed to assess perioperative nutritional and immunological risk in patients undergoing gastrointestinal surgery[149] . In their study, the score showed strong and independent predictive ability for the occurrence of post-TIPS HE (OR = 7.3; 95% CI: 2.1–25.6; p = 0.002).

Among nutritional alterations, muscle mass loss has been most extensively investigated. Sarcopenia is frequent at the time of TIPS placement, with a reported prevalence of nearly 50%[150]. Vanderschueren et al. retrospectively documented a detrimental impact of sarcopenia, measured by transverse psoas muscle thickness (TPMT)/length, on both mortality (53.4% vs. 22.3%, p < 0.001) and overall complications (74.1% vs. 57.9%, p = 0.04)[151]. Similar findings were reported by Stoffel E. and colleagues, showing that sarcopenia was independently associated with reduced 1-year survival after TIPS (HR 2.435; 95% CI 1.346–4.403), even after adjustment for confounders[152].

More recently, sporadic evidence has been collected on the prognostic impact of sarcopenia on post-TIPS survival. A German group employed artificial intelligence for the automatic retrospective evaluation of muscle mass and adiposity in 195 L3 CT-scans using an AI-based software tool (Visage version 7.1, Visage Imaging GmbH, Berlin, Germany) powered by a convolutional neural network[153]. Their results confirmed that sarcopenia was associated with higher rates of post-interventional complications (HR 1.67; 95% CI: 0.95–2.93), increased incidence of HE (HR 1.65; 95% CI: 0.81–3.33), and reduced 1-year survival (HR 1.39; 95% CI: 0.66–2.92).

Nardelli S et al., have clearly demonstrated that the presence of baseline sarcopenia was independently associated with higher risk of HE in 46 consecutive patients undergoing TIPS placement (sHR, 31.3; 95% CI, 4.5-218.07; P < .001)[154]. Considering the higher risk of HE in malnourished patients, Gairing SG and colleagues have proposed to provide a global evaluation in patients candidable for TIPS placement, including sarcopenia assessment. Moreover, the authors have

proposed to assess a prophylaxis strategy before TIPS procedure in order to prevent post-TIPS HE, that include the use of under-dilatated stent grafts, premedication with rifaximin and nutritional support with dedicated diet in order to maintain sufficient calorie intake of about 35–40 kcal/kg body weight/day and protein intake of about 1.2–1.5 g/kg body weight/day with a focus on plant- based proteins[155]. Despite these nutritional indications having a theoretical basis, no clinical trials have actually demonstrated the efficacy of the nutritional support before TIPS placement. Praktiknjo et al., also showed that sarcopenia, retrospectively measured with sex-specific TPMT/height cut offs in 186 patients, is associated with higher risk of persistent ascites, HE, ACLF and mortality after TIPS, with a clear association with higher levels of systemic inflammation assessed by e Chronic Liver Failure Consortium Acute Decompensation (CLIF-AD) score[156]. These results were confirmed also in asiatic population, in which a retrospective study has examined the role of TMTP/height score in identifying population at higher risk of post-TIPS HE and mortality[157]. A recent paper has tried to summarize the available evidence. This systematic review, including 22 studies and over 70,000 patients, demonstrated that pre-TIPS malnutrition and sarcopenia are consistent independent predictors of adverse outcomes, particularly post-TIPS hepatic encephalopathy and mortality[158]. However, the analysis is limited by the predominance of retrospective designs and only 2 studies on 22 were reported as being prospective; actually both studies enrolled consecutive patients but the analysis were retrospectively conducted. As a result, no studies have been prospectively designed with the aim of exploring the prognostic impact of sarcopenia. Moreover, heterogeneity in the definitions and measurements of nutritional status, and variable follow-up and outcome criteria make it even more difficult to extract solid evidence from these studies.

Regarding muscle quality, current evidence remains limited. The role of myosteatosis in post-TIPS clinical outcomes has been explored in only a few studies. Shi et al. retrospectively demonstrated that the presence of myosteatosis, assessed two weeks before TIPS on the L3 CT slice, was independently associated with a higher risk of post-TIPS HE (OR 2.372, 95% CI 1.268–4.438), regardless of sarcopenia and other prognostic factors[159]. Similarly, an Asian study evaluated myosteatosis using psoas muscle attenuation (PMA), both alone and in combination with sarcopenia. The results showed that while myosteatosis alone increased the risk of post-TIPS HE, the greatest effect was observed in the presence of combined sarco-myosteatosis;

moreover, PMA remained significantly associated with post-TIPS mortality in multivariate analysis[157]. Li et al. investigated the psoas muscle fat index (PMFI), defined as the ratio between psoas muscle area (PMA) and psoas muscle density (PMD), with higher values reflecting greater muscle fat content[160]. In 155 patients with viral-related cirrhosis retrospectively enrolled, survivors showed significantly higher PMFI values compared to non-survivors (43.7 vs. 37.0 mm²/HU, $p = 0.038$), and this association with post-TIPS mortality persisted after adjustment for competing factors (HR 1.159, 95% CI 1.063–1.263, $p < 0.001$). Conversely, another retrospective study demonstrated that reduced PMD alone was sufficient to identify patients at increased risk of post-TIPS mortality[161].

Adiposity may significantly influence outcomes following TIPS placement. Dysregulation in adipose tissue distribution and quality has been linked to metabolic and pro-inflammatory pathways, which may negatively impact the response to interventional procedures such as TIPS. Despite this, few studies have systematically investigated the predictive value of VAT and SAT distribution for post-TIPS events. Cheng et al. conducted a retrospective multicenter study using machine learning to analyze VAT at the L3 level on CT scans, developing a predictive model for post-TIPS HE. The model demonstrated a specificity of 0.63 and a negative predictive value of 1.00, with a sensitivity of 0.60 and a positive predictive value of 0.75[162]. A more comprehensive analysis was performed by Wang and colleagues, who evaluated both the Visceral Adipose Tissue Index (VATI, normalized for height) and Subcutaneous Adipose Tissue Index (SATI) in relation to post-TIPS HE. Their sex-specific analysis revealed that VATI was a significant predictor in males ($p = 0.033$), whereas SATI was significant in females ($p = 0.003$). Notably, male patients with low VATI (< 53.52 cm²/m²) had an increased risk of post-TIPS HE (OR 6.44; 95% CI 1.72–23.59; $p = 0.006$), while female patients with low SATI (< 70.05 cm²/m²) were also at higher risk (OR 10.55; 95% CI 2.36–46.23; $p = 0.002$)[163].

Available evidence indicates that the relationship between TIPS and nutrition is bidirectional. On the one hand, unfavorable changes in muscle mass and adiposity can negatively influence prognosis after TIPS; on the other hand, TIPS placement has been associated with improvements in nutritional status. Theoretically, the diversion of portal blood into the systemic circulation increases hyperammonemia, thereby enhancing the risk of hepatic encephalopathy. Hyperammonemia is known to

activate the myostatin pathway and impair muscle proteostasis[58]. Nevertheless, several studies have reported muscle gain and even reversal of sarcopenia following TIPS. The reduction of portal hypertension and its complications, in particular ascites-related anorexia, decreases conditions that place patients at risk of malnutrition. Moreover, TIPS has been shown to attenuate chronic systemic inflammation, a major driver of clinical deterioration and malnutrition in cirrhosis[164]. Improvement in intestinal absorption due to reduced portal hypertension has also been observed.

Historically, Trotter et al. first suggested in 1998 that TIPS may increase lean body mass, reflecting an overall improvement in clinical status[165]. More recently, Gioia et al. demonstrated an increase in skeletal muscle index and muscle attenuation after TIPS, together with a more favorable adipose tissue profile, characterized by reduced visceral fat and improved subcutaneous fat[166]. Similar findings have been reported by other groups, mostly in retrospective studies, and summarized in systematic reviews[150,168]. However, meta-analyses remain limited due to heterogeneity in study design, definitions, methods, and outcome measures.

Muscle gain appears to occur more frequently in patients with more severe baseline sarcopenia. Huang et al. identified lower pre-TIPS SMI (OR 0.93, 95% CI 0.87–0.99, P = .031) and reduction in portal pressure gradient (OR 1.13, 95% CI 1.03–1.24, P = .009) as independent predictors of substantial post-TIPS muscle mass improvement[169]. Several longitudinal studies have also demonstrated the clinical relevance of these changes. In particular, Liu et al.[170] and Tuifua et al.[171] showed that patients who recovered muscle mass experienced fewer complications, lower mortality, and reduced risk of HE. Gioia et al. further linked muscle gain to improvements in cognitive function and quality of life[172]. Conversely, persistent sarcopenia or sarcopenic obesity, as highlighted by Ronald et al.[173], was associated with worse outcomes. Collectively, these findings support the concept that reversal of sarcopenia after TIPS has significant prognostic implications.

In conclusion, despite growing evidence, several limitations affect our understanding of the nutritional impact of TIPS. Most available studies are retrospective, monocentric, and based on relatively small cohorts, limiting generalizability. Heterogeneity in imaging techniques, cut-offs, and definitions of sarcopenia or myosteatosis makes comparison across studies difficult. Follow-up periods are often

short, preventing firm conclusions on long-term trajectories of muscle and fat compartments. In addition, few studies adjust for confounders such as ongoing liver disease progression, physical activity, or dietary intake. Finally, evidence is scarce on whether improvements in body composition after TIPS translate into consistent survival benefits across different patient subgroups.

STUDIES

During my PhD, I contributed to several publications focused on liver cirrhosis, particularly examining the role of nutrition and its impact on patient prognosis. The main PhD project was titled *"Effect of Body Composition on Prognosis in Patients with Cirrhosis Undergoing TIPS Placement."* To address this topic, we initiated a multicenter prospective study investigating how body composition influences the clinical course of liver cirrhosis. This work led to our first manuscript, published in the *Journal of Hepatology* under the title *"Myosteatosis Is Closely Associated with Sarcopenia and Significantly Worse Outcomes in Patients with Cirrhosis." (Figure 1)*[174].

In parallel, we reviewed the existing literature on body composition in the setting of TIPS procedures and how TIPS may affect nutritional status over time. Due to substantial heterogeneity in study design and diagnostic criteria for muscle changes, a meta-analysis was not feasible. Nevertheless, we published a systematic review in *Nutrients*, titled *"The Impact of Transjugular Intrahepatic Portosystemic Shunt on Nutrition in Liver Cirrhosis Patients: A Systematic Review."*[175]

Based on the conclusions of this review, we initiated a multicenter prospective study entitled *"Prognostic Impact and Assessment of Nutritional Changes in Patients with Liver Cirrhosis Undergoing Transjugular Intrahepatic Portosystemic Shunt (TIPS): A Prospective Study."* We are currently finalizing the manuscript for submission.

STUDY 1 - Myosteatosis is closely associated with sarcopenia and significantly worse outcomes in patients with cirrhosis

M1.1 RATIONALE

Previous studies exploring muscle alterations in cirrhosis have been mostly retrospective, monocentric, and limited to patients with advanced disease awaiting transplantation. In addition, sarcopenia and myosteatosis have often been evaluated separately, and different, non-standardized methods have been used to define sarcopenia, limiting comparability across studies. Functional performance and frailty were also rarely assessed, despite their recognized clinical relevance. To overcome these limitations, we designed a prospective, multicenter study in a broader cirrhotic population, simultaneously assessing sarcopenia and myosteatosis, incorporating muscle function and frailty tests, and applying computed tomography — the gold standard — for body composition analysis.

S1.2 METHODS

Study aims and design

The primary aim of the study was to investigate the impact of sarcopenia and myosteatosis, alone or in combination, on mortality, the need for hospitalization, and first or further liver decompensation. The secondary aim was to explore the correlations among muscle function, frailty and sarcopenia and myosteatosis in the subgroup of patients with available data.

Consecutive patients with cirrhosis from 26 Italian centres were prospectively enrolled between January 2019 and December 2021 and followed-up for 1 year. The onset of the SARS-CoV-2 pandemic during the enrolment period significantly limited recruitment resources, especially from smaller centres. The cumulative incidence of the outcome of interest was calculated by competing risk analysis, and the prognostic role of muscle changes was assessed by multivariable analysis adjusted for major known prognostic indicators.

Eligibility and inclusion criteria

All patients with cirrhosis aged 40-75 years who underwent an abdominal computed tomography (CT) scan of the third lumbar (L3) vertebra for any clinical indication

were eligible for the study. The cut-off age for inclusion was an arbitrary decision to reduce the potential confounding effect of age-related muscle abnormalities. We excluded patients on LT waiting lists or who had hepatocellular carcinoma (HCC), a history of LT, concomitant neuromuscular disease, current malignancy other than non-melanocytic skin cancer, a history of serious extrahepatic diseases, or HIV infection. Each patient was enrolled at the time of abdominal CT scan.

Patient characteristics and follow-up

Patient characterisation at inclusion was based on the following data: age, sex, liver disease aetiology, the presence and grade of ascites according to the International Club of Ascites, presence and grade of overt hepatic encephalopathy (OHE) according to the West Haven criteria, animal naming test (ANT) result of patients without OHE, oesophageal varices and size (according to the American Association for the Study of Liver Disease classification), history of gastrointestinal bleeding, and model for end-stage liver disease (MELD), MELD-Na and Child–Pugh scores.

Anthropometric data (including dry weight for patients with ascites and fluid retention) and hand grip test (HGT), liver frailty index (LFI) and ‘timed up and go’ (TUG) test results were also recorded.

Clinical visits to the outpatient clinic and biochemical exams were repeated at 6 and 12 months or more frequently when needed. During follow-up, data on hospitalizations and episodes of liver decompensation were collected during inpatient and outpatient visits, as well as through phone calls or emails.

The first episode of liver decompensation was defined as the presence of ascites, OHE, or variceal bleeding in a previously compensated patient. 'Further decompensation' was defined as the worsening of previous decompensation with recurrent, refractory, or complicated ascites; acute kidney injury; spontaneous bacterial peritonitis; variceal bleeding; or worsening of OHE. Death from any cause and LT were also recorded during the observation period.

Assessment of muscle changes

The assessment of sarcopenia and myosteatosis on CT images was centralised at the coordinating centre. All CT scans were assessed for sarcopenia and myosteatosis by two trained experts (S.DC. and L.L.).

According to the consensus statement of the EWGSOP (European Working Group on Sarcopenia in Older People)[176], abdominal muscle area was always evaluated by CT at the third or fourth lumbar vertebra in the present study. The Hounsfield unit (HU) limits used for assessing skeletal muscle mass ranged from -29 to +150 HU. The muscle area was normalised for height, resulting in a ratio (cm2/m2) known as the L3–L4 skeletal mass index (L3–L4 SMI). Patients were classified as having sarcopenia according to the validated SMI cut-off (<50 cm2/m2 for men and < 39 cm2/m2 for women).[124]

To assess myosteatosis across the entire muscle area, we computed the mean muscle attenuation in HU, which reflects the fat infiltration of muscles. We used the same CT image used for the SMI calculations. Patients were classified as having myosteatosis according to the following cut-off values: <41 HUs for patients with a BMI <24.9 kg/m2 and <33 HU for those with a BMI ≥25 kg/m2[132].

The adipose tissue located within the peritoneal cavity was identified using HU thresholds for visceral adipose tissue ranging from -150 to -50 HU (PMID: 8782734). Subcutaneous adipose tissue was detected in the layer of adipose tissue beneath the skin and above the parietal peritoneal lining, using HU thresholds ranging from -190 to -30 HU. (PMID: 3710689)

Assessment of muscle function and frailty

Assessment of patient muscle function at enrolment was based on the TUG test[177]and the HGT[178] Patient frailty was assessed using the LFI[73]. Patients with LFI ≥4.5 were categorised as frail, those with LFI ≥3.2 and <4.5 were categorised as prefrail, and those with LFI <3.2 as non-frail.

Study approval and informed consent

The Local Ethical Committee of the Coordinator Center approved the study protocol and data collection (EC n° 94/19, 30/01/19), and each collaborating centre provided its own ethical committee approval. All patients provided informed consent to participate in the study.

Statistical analysis

Baseline patient characteristics are reported as proportions or means and standard deviations. The chi-square test assessed differences between proportions, and the

Student's t test evaluated differences between means. We calculated the incidence rates of the events of interest as the number of observed events/100 patient-years of follow-up.

We assessed the cumulative incidence function (CIF) of death by competing risk analysis, with LT as a competing event. Death and LT were considered competing events when assessing the CIF of first and further liver decompensation and of new hospitalizations. CIF differences were assessed by Gray's test. Time zero for analyses of time to events (death, first or further decompensation and new hospitalization) was the date of the index CT for muscle assessment.

One-year incidence plots are shown. Throughout the text and figures, probabilities are expressed as percentages.

We assessed the adjusted impact of muscle damage on outcomes by a multivariable Fine-Gray model for competing risks. We used Robust (sandwich) variance estimation for multivariable models The analysis included the following known prognostic indicators: sarcopenia, myosteatosis, serum bilirubin, INR, serum albumin, serum creatinine, age, sex, and the presence of OHE or ascites. The MELD and Child-Pugh scores were included in separate analyses excluding their individual components to avoid redundancy. A variable indicating participating centre was included in all multivariable models to account for between-centre heterogeneity. We performed variable reduction for the final multivariable models by a backwards procedure, based on the importance of risk predictors, clinical judgement and statistical significance. We included the number of variables in the multivariable models ≤1 per 10 observed outcome events.

In a subgroup of patients with available information on muscle function, we explored the relationships between HGT, TUG test and LFI results with muscle surface and muscle attenuation at the time of CT scan using regression analyses.

Statistical analyses were performed using STATA 16.1 (©2019 Stata Corporation, College Station, TX).

S1.3 RESULTS

Patient characteristics at inclusion and type of skeletal muscle damage

A total of 447 patients were eligible for the study, 14 of whom were excluded due to incomplete data, leaving 433 patients with available data for analysis. The mean follow-up (±SD) was 349±89 days.

The characteristics of the patients in the total population and in the subgroups according to the type of muscle changes are shown in Table 1.

The most common aetiology of cirrhosis was alcohol-related (39.9%), followed by hepatitis C (15.5%) and metabolic (15.0%). At enrolment, 158 patients were compensated, and 275 patients were decompensated, owing to ascites, OHE or portal hypertensive bleeding alone or in various combinations. The mean MELD score was 13±4.95 points, and the mean Child–Pugh score was 7.45±2.0 points; 162 patients (37.4%) were in class A, 196 (45.3%) in class B, and 75 (17.3%) in class C.

Isolated sarcopenia (I-sarcopenia) was diagnosed in 36 patients (8.3%), isolated myosteatosis (I-myosteatosis) in 166 patients (38.3%) and combined sarcopenia and myosteatosis in 135 patients (31.2%), while only 96 patients (22.2%) had no evidence of muscle damage (Fig. 1). Muscle changes were significantly more common in females than in males (88.8% vs. 73.4%, p <0.0001), mainly due to a significantly greater prevalence of I-myosteatosis in females (52.0% vs. 32.8%, p <0.0001) (Fig. S2). Overall, patients with any muscle changes had more advanced disease, with significantly greater Child–Pugh scores (7.6±2.0 vs. 7.0±1.8 points, p = 0.01) and a greater prevalence of ascites (53.4% vs. 36.5%, p = 0.003). Myosteatosis was the most frequent muscle change, detected in 301 patients (69.5%). Compared to I-sarcopenia patients and patients without muscle changes, patients with myosteatosis were significantly older (60.8±8.8 vs. 57.2±9.1 years, p = 0.0001) and had significantly higher MELD (13±5 vs. 12±4 points, p = 0.006), Child–Pugh (7.6±2.1 vs. 7.0±1.8 points, p = 0.006) and ANT (18.5±5.5 vs. 16.5± points, p = 0.0037) scores. Comparisons between patients with and without myosteatosis, independent of the presence of sarcopenia.

Patients with I-myosteatosis also had greater visceral and subcutaneous adiposity than patients with myosteatosis and sarcopenia (170±100 cm/m2 vs. 131±79 cm/m2, p = 0.0005) (Table 2). Muscle function assessment was not always available, as some centres did not have a suitable handgrip dynamometer, which preventing LFI assessment in many patients. Specifically, we collected HGT results for 274 patients

(63.3%), TUG test results for 228 patients (52.6%), and LFI results for 249 patients (57.5%). Compared to patients without myosteatosis, those with myosteatosis, either alone or associated with sarcopenia, had worse TUG test (13.3±5.7 vs. 9.4±3.8 points, p value <0.0001) and HGT (32.5±16.4 vs. 36.8±15.9 points, p = 0.049) results and were more frequently diagnosed as frail (33% vs. 13%, p = 0.002).

Impact of muscle changes on mortality

During the follow-up period, 51 deaths occurred, 45 of which were liver related. The major outcome events and corresponding incidence rates/100 patient-years are shown in Table 1. The incidence of death was higher in patients with muscle changes than in those without muscle changes. The difference was statistically significant for patients with I-myosteatosis (p = 0.015) and those with combined sarcopenia and myosteatosis (p = 0.012). The corresponding 1-year cumulative incidences of death with LT as a competing risk were 5.6% for patients without muscle changes, 5.2% for patients with I-sarcopenia, 13.8% for patients with I-myosteatosis and 13.4% for patients with combined sarcopenia and myosteatosis (Fig. 2). The differences between patients in each muscle change group and patients without muscle changes were, however, not significant, although the increase in mortality in patients with combined sarcopenia and myosteatosis approached significance (p = 0.079).

Impact of muscle changes on hospitalization

During the 1-year follow-up, 207 liver-related hospitalizations were reported. The hospitalization incidence rate/100 patient-years in patients with combined sarcopenia and myosteatosis and I-myosteatosis was 55.7 and 55.2, respectively, both significantly higher (p = 0.0012 and 0.025, respectively) than that in patients without muscle changes (34.7). In patients with I-sarcopenia, the corresponding incidence rate was 47.2, which was not significantly different from that in patients without muscle changes (Table 1). The 1-year cumulative incidence of new hospitalization with death and LT as competing events was also significantly greater in patients with any type of muscle change than in those without muscle changes (Fig. 3).

Impact of muscle changes on first and further liver decompensation

At the start of the study, 158 patients with compensated cirrhosis were included, 43 without muscle changes, 12 with I-sarcopenia, 66 with I-myosteatosis and 37 with combined sarcopenia and myosteatosis.

Overall, decompensation occurred for the first time during follow-up in 5 of the 43 patients without muscle changes and 19 of the 115 patients with any type of muscle changes, with corresponding incidence rates per 100 patient-years of 11.3 and 16.7, respectively (p = 0.39). Among the 275 patients with decompensated cirrhosis at inclusion, 119 developed further decompensation: 19 of 53 without muscle changes, 11 of 24 with sarcopenia, 45 of 100 with myosteatosis, and 44 of 98 with combined sarcopenia and myosteatosis. The corresponding incidence rates per 100 patient-years were 37.6, 46.4, 50, and 48.9, respectively (p was not significant for differences between each type of change vs. no changes). In the overall population, the 1-year cumulative incidence of any decompensating event (either first or further, with death and liver transplant as competing events) was 39% for patients with combined sarcopenia and myosteatosis, 36% for those with I-sarcopenia, 34% for those with I-myosteatosis, and 30% for those with no muscle changes (Fig. 4). Compared with patients with no changes, the difference was significant for those with combined sarcopenia and myosteatosis (p = 0.018) and for those with I-sarcopenia (p = 0.046).

Adjusted prognostic role of muscle changes

To investigate whether muscle changes had an independent impact on outcomes, we performed multivariable analyses. Multivariable models exploring the prognostic impact of muscle changes including MELD are shown in Table 3. Muscle changes had a significant effect on the incidence of hospitalization (p = 0.012) and tended to increase mortality (p = 0.058) but had no effect on first or further liver decompensation (p = 0.60). The c-statistic of the attenuation index for mortality was 0.69 (CI 0.62-0.76). In models including the individual components of the MELD score (ascites, OHE, and albumin) , no independent prognostic effect of muscle changes was observed.

Correlations between muscle function and sarcopenia and myosteatosis

The frailty index was assessed in 238 patients, and the mean frailty index score was 3.7±0.85 points. A total of 65 patients were classified as frail, and 117 as prefrail. The mean frailty index score was significantly higher in patients with combined sarcopenia and myosteatosis (3.96±0.84) or I-myosteatosis (3.83±0.88) than in patients with I-sarcopenia (3.5±0.6) or no muscle changes (3.49±0.82). Differences in the same direction were found for HGT and TUG test results (Table 2). The HGT

values correlated with the SMI ($r = 0.11$, $p < 0.0001$) but not with the HU (muscle attenuation utilised for the diagnosis of myosteatosis as a continuous value), while the TUG test and LFI did not correlate with the SMI but were inversely correlated with the HU (Fig. S3).

S1.4 DISCUSSION

In the present study, we aimed to assess the prognostic relevance of muscle alterations in a large prospective cohort of patients with cirrhosis and varying degrees of liver impairment.

Seventy-eight percent of patients had some muscle changes at the time of enrolment. In our cohort, myosteatosis was the main muscle alteration affecting a significant proportion of the study population, while sarcopenia was rarely present in the absence of myosteatosis. In a retrospective cohort, Tachi et al.[179] reported a prevalence of myosteatosis of 82% and sarcopenia of 36%, with 93% of patients with sarcopenia having concomitant myosteatosis. Only a small proportion of patients had sarcopenia alone, as in our study. A recent study[82] examined the combination of reduced muscle function, quality, and quantity in 197 patients and suggested that myosteatosis may precede the onset of other muscle abnormalities. There may be a physiological explanation for this observation. Chronic hyperammonaemia, present in cirrhosis, induces mitochondrial dysfunction and a subsequent reduction in lipid oxidation, leading to intramuscular fat infiltration (myosteatosis)[110]. Intramuscular fat, often associated with insulin resistance, has been linked to the development of a lipotoxic profile associated with the secretion of fatty acids and inflammatory adipokines, the latter having a detrimental effect on myocyte function[180].

In our cohort, patients with myosteatosis, with or without sarcopenia, were generally older, more often female, had more visceral and subcutaneous fat, and had more advanced liver disease (see Table 1). In addition, these patients exhibited lower cognitive performance (as measured by the ANT) and were more likely to have ascites and bacterial infections. Functional performance was also impaired in these patients, as evidenced by lower TUG test scores and a greater tendency to frailty.

The role of myosteatosis, which has not always been evaluated in previous studies, was relevant in blunting that of sarcopenia, which has always been considered an important predictor of clinical outcomes in patients with cirrhosis.

Indeed, a diagnosis of myosteatosis, even if not associated with sarcopenia, was a predictor of a greater risk of death (Fig. 2) and hospitalization (Fig. 3).

On the other hand, I-sarcopenia was not an independent predictor of mortality or hospitalization in our cohort. This finding may be influenced by the limited number of patients diagnosed with I-sarcopenia.

Our study highlights that the occurrence of muscle changes, regardless of the type, represents a significant moment in the natural history of cirrhosis and adversely affects numerous outcomes. Multivariate analyses of competitive risk factors for mortality (with LT as a competing event), including the presence and type of muscle abnormalities, the MELD score and the presence of OHE or ascites (Table 3), showed that the presence of muscle changes negatively affected survival and hospitalization rates.

Altered muscle function and frailty have been shown to affect quality of life[181], self-autonomy and prognosis of patients with cirrhosis[69]. In our study, many patients were categorised as frail or prefrail (76.5% in total). The correlation between frailty and TUG test results and muscle attenuation suggests that these tests, which are easy to perform, may be useful surrogates that overcome the need for imaging to assess changes in muscle quality.

The strengths of the present study include its prospective design, multicentre structure, use of CT scans (the gold standard for detecting muscle changes) in all patients, and detailed analysis of various types of muscle abnormalities.

Our study has several limitations. Nutritional assessment was only performed at baseline, without considering changes that may have occurred during follow-up. The different centres' policies regarding patient care in day services or in hospitals may have influenced the hospitalization rate, and laboratory data were not centralised. Muscle function tests were not performed in any of the centres participating in the study. Furthermore, although CT scans are widely used in patients with cirrhosis for various reasons, the availability of CT scans as an inclusion criterion may have

introduced a baseline selection bias. Moreover, the prevalence of muscle alterations was sex dependent. Indeed, male patients represented 70% of the population, which could have impacted the overall cohort's distribution averages. Consequently, the study outcomes may not fully represent both sexes, highlighting the need for future larger studies designed with this in mind.

In conclusion, our study has shown that a comprehensive and integrated assessment of muscle changes is crucial for understanding their role in the natural history of cirrhosis. Our analyses revealed that myosteatosis is the most frequent alteration and has a significant impact on the course of liver disease. Many previous studies have focused on the assessment of sarcopenia, but concomitant myosteatosis is likely to play a major prognostic role. This may resize the predictive role of sarcopenia in favour of a more comprehensive consideration of muscle changes.

Our study suggests that muscle function tests could serve as a valuable and practical bedside tool for estimating prognosis and identifying patients at greater risk of mortality.

STUDY 2 - The Impact of Transjugular Intrahepatic Portosystemic Shunt on Nutrition in Liver Cirrhosis Patients: A Systematic Review

S2.1 RATIONALE

TIPS has become a cornerstone in the management of complications of portal hypertension, yet its nutritional implications are far less well defined. Despite a large body of literature on clinical and prognostic outcomes, only a few systematic reviews or meta-analyses have attempted to synthesize the evidence on post-TIPS nutritional changes. Data on longitudinal trajectories of muscle mass and quality are particularly scarce, and most available studies are retrospective, single-center, and heterogeneous in design. Moreover, sarcopenia and adiposity have often been assessed separately, without accounting for their combined prognostic impact. These gaps highlight the need for an integrated evaluation of nutritional outcomes after TIPS to better identify patients who may benefit most from the procedure.

S2.2 METHODS

The PICO framework was followed to define the review question's key elements. The reporting of this systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**http://www.prisma-statement.org** (accessed on 14 December 2022)[182].

S2.2.1. Literature Search

The MEDLINE (PubMed), Scopus, Web of Science, and Cochrane library databases were comprehensively searched from inception to 14 December 2022. A literature review was created using the following terms (with corresponding variations): ((cirrhosis (MeSH Terms) OR (ascites) OR (hepatic encephalopathy) OR (cirrhotics)) AND (Portosystemic Shunt, Transjugular Intrahepatic (MeSH Terms)) AND ((Nutritional Status (MeSH Terms)) OR (nutritional) OR (albumin) OR (BMI) OR (total body mass) OR sarcopenia OR (body composition) OR (body weight))). Medical Subject Headings (MeSH) were used to increase the precision and efficiency of the search. Additionally, we manually checked the reference lists of the

included studies (or relevant review articles) and performed a backward citation analysis.

S2.2.2. Criteria for the Selection of Studies

Inclusion criteria for the studies consisted of evaluations of patients diagnosed with liver cirrhosis who underwent TIPS placement, regardless of the indication for the procedure. Additionally, the studies were required to assess changes in nutritional status of the patients prior to and following TIPS insertion. The exclusion criteria for the studies consisted of any abstracts, studies that utilized animal models, case reports, and correspondence letters. Additionally, the scope of the literature search was restricted to articles written in the English, German, Italian, and Spanish languages.

S2.2.3. Study Selection, Data Extraction, and Data Calculation

A standardized data extraction sheet was developed, and subsequently underwent pilot testing to ensure its reliability. Two investigators independently performed a literature review, utilizing titles and abstracts as initial screening criteria (JG, SK). Eligible full-text articles were subsequently assessed, and relevant data were extracted by the investigators (JG, SK). The extracted information was then reciprocally compared between the investigators (JG, LP, SD, SK). Any discrepancies in study selection or data extraction were resolved through a consensus process, with the assistance of a senior hepatologist (MM).

The following pre-determined data points were extracted from each eligible study: (1) First author's name, (2) Year of publication, (3) Study design, (4) Time frame of the study, (5) Patient exclusion criteria, (6) Sample size, (7) Characteristics of the study participants, (8) Indication for TIPS procedure, (9) Characteristics of the TIPS procedure, (10) Portal pressure gradient post-TIPS procedure, (11) Follow-up duration, (12) Measures of evaluating nutritional status, and (13) Change in nutritional status. In instances where the authors did not directly report the change in nutritional status, it was calculated from the available information, if feasible.

S2.2.4. Risk of Bias Assessment

The risk of bias is evaluated using the ROBINS-I guidelines, which identify seven domains and classify the risk as low, moderate, serious, or critical. A low risk of bias indicates that the study is similar to a well-conducted randomized trial, while a critical risk indicates significant problems with the study (https://doi.org/10.1136/bmj.i4919).

S2.3. RESULTS

A comprehensive search of four major medical databases (MEDLINE, Scopus, Web of Science, and Cochrane) yielded a total of 1412 records. A total of 373 duplicate records were subsequently removed. Of the remaining 1039 records, 62 were evaluated in full-text, and 47 were excluded based on pre-determined exclusion criteria (as detailed in Figure 5). Additionally, 723 additional records were identified through backward citation analysis. In total, 15 records were finally included in the present study (as illustrated in Figure 5).

In the present study, a total of 15 studies were included (Table 4), which were published between 1998 and 2022, and altogether followed 850 patients. Of these, seven studies (47%) were retrospective in design[166,183-187,] three studies (20%) were prospective[188-190], and five studies (33%) did not disclose this information[190-194]. In the majority of the studies, the sample population consisted of all consecutive patients, with exclusion criteria based on cardiac, renal, hepatic, or pulmonary function, as well as a history of malignancy. The most frequent underlying chronic liver disease was alcohol-related liver disease (in 10 out of 15 included studies; 67%). The sample sizes of the included studies varied between 11 and 224 patients, and the mean or median age of the patients varied between 54.1 and 60 years, with male patients predominating in all studies. The indications for TIPS insertion were refractory ascites and variceal bleeding. The most frequently used stent material was polytetrafluoroethylene (PTFE); however, some older studies employed bare metallic stents. The proportion of patients with TIPS dysfunction was reported infrequently[183,184]. In instances of dysfunction detection, intervention in the form of TIPS revision was implemented to re-establish patency. Non-responsive cases were excluded from the original studies. The post-TIPS portal pressure gradient varied between studies, ranging from 6.0 to 15.5 mmHg. Furthermore, the time point at

which the change in nutritional status was measured varied between 2 and 36 months after TIPS insertion.

S2.3.1. Risk of Bias Assessment

In this systematic review, we did not assess the risk of bias related to deviations from the intended interventions. We found a critical risk of bias due to confounding, as none of the studies controlled for variables such as caloric intake or the frequency and intensity of physical exercise. On the other hand, the risk of bias due to participant selection was low, as all eligible and consecutive patients were included. The risk of bias related to the classification of interventions was also low. The risk of bias due to missing data was moderate in some studies, as a number of patients were lost to follow-up. However, the risk of bias related to the measurement of outcomes was critical, as most evaluators of nutritional status were not blinded to the intervention. Lastly, we did not detect any evidence of selective reporting of results (Figure 6).

The subsequent section of the results is divided into three distinct sub-sections. The first sub-section presents the changes in Body Mass Index (BMI), weight (W), and/or body cell mass (BCM). The second and third sub-sections present the changes in body composition with regard to alterations in muscle and fat tissue, respectively.

S2.3.2. Body Mass Index, Weight, and/or Body Cell Mass

In total, 11 studies reported on changes in Body Mass Index (BMI, kg/m2), weight (W, kg), and/or body cell mass (BCM, kg) (Table 4). These measures were evaluated in patients with no ascites (following peritoneal paracentesis) or were adjusted for ascites volume. Of these studies, six reported a significant improvement in BMI or W with two studies noting improvement in BCM only (the increase in BMI/weight was in these cases statistically not significant). Two studies that specifically distinguished between underweight or sarcopenic patients and those who were overweight or nonsarcopenic reported a significant improvement in nutritional status in the former group[184]. Finally, only one study failed to report an improvement in such measures.

S2.3.3. Skeletal Muscle Volume, Skeletal Muscle Function

A total of seven studies reported on changes in skeletal muscle volume and skeletal muscle function (Table 4). The mid-arm muscle area (MAMA) was quantitatively determined using a flexible tape measure. To further assess muscle mass, axial computed tomography (CT) images were obtained at an L3 vertebra height through the abdomen and utilized to calculate skeletal muscle areas (SMA)

These muscle areas were then normalized to height, resulting in the calculation of the skeletal muscle index (SMI). Additionally, both transversal right psoas muscle thickness at the umbilical level/height (TPMT/height in mm/m) and total psoas muscle area (TPMA in mm2) were also reported in the study by Artru et al. [183]. All studies measuring changes in skeletal muscle volume reported a significant improvement, with Liu et al. confirming this trend specifically in sarcopenic patients 184. The SMA increased by a minimum of 6.6 cm2 within 12 months after TIPS placement[185,190]. This increase was even more pronounced in sarcopenic patients, with an increase of up to 20 cm2[184]. The improvement in SMI ranged between 2.39 and 5.8 cm2/m2, with sarcopenic patients showing an even greater improvement of approximately 8 cm2/m2 within 10–19 months after TIPS placement [13,166,184]. Additionally, both the TPMT and TPMA significantly improved within 6 months of TIPS placement [183]. On the other hand, the study conducted by Allard et al. found that there was no improvement in measures of skeletal muscle function, such as muscle relaxation rate and muscle force [191].

S2.3.4. Adipose Tissue Volume

In a total of nine studies, changes in the quantity of adipose tissue were evaluated (Table 4). To assess adipose tissue quantity, axial computed tomography (CT) images were obtained at an L3 height through the abdomen. The volume of subcutaneous adipose tissue (SAT, adipose tissue below the skin but above the parietal peritoneal lining in cm3/3 mm) and visceral adipose tissue (VAT, intraperitoneal adipose tissue in cm3/3 mm) were estimated[190.] Furthermore, adipose tissue areas were normalized to height, resulting in the estimation of the tissue area indices—subcutaneous adipose tissue index and visceral adipose tissue index (SATI and VATI in cm2/m2)183. Subcutaneous and visceral fat surfaces (SFA and VFA in cm2, respectively) were also calculated[183,184]. Additionally, Liu et al. quantified subcutaneous fat thickness (SFT in mm)[184]. Fat mass (% of body weight or in kg) was estimated using calorimetry. Finally, Plauth et al. quantified the mid-arm fat area using a skinfold caliper (MAFA in cm2)[188]. In the reviewed studies, no significant change was observed in measures of fat mass (measured using calorimetry, except an increase in the study by Allard et al.) or in the mid-arm fat area. However, a significant expansion of subcutaneous fat tissue was observed in all studies[166,183,184,] with the exception of one study[190]. Additionally, a notable reduction in visceral fat tissue was reported in two studies, while remaining unchanged in one study.

S2.4 DISCUSSION

TIPS placement is a commonly utilized therapeutic intervention for individuals with liver cirrhosis and associated complications of portal hypertension, including refractory ascites and variceal bleeding. This intervention has been demonstrated to significantly improve overall survival in these patients, as evidenced by several clinical studies [195-196]. Despite these benefits, malnutrition, which is prevalent among cirrhotic individuals, has been linked to adverse outcomes after TIPS placement, such as hepatic encephalopathy, acute-on-chronic liver failure (ACLF), and mortality. On the other hand, some studies have suggested an improvement in the nutritional status following TIPS placement in cirrhotic patients. Therefore, the aim of this systematic review was to evaluate changes in nutritional status that occur after TIPS placement in patients with liver cirrhosis.

This review analyzed data from 15 studies (comprising a total of 850 patients) that were published between 1998 and 2022. The number of participants per study ranged from 11 to 224, with the majority being men. Most of the participants in these studies had alcohol-related liver disease. Alcohol consumption has a multifactorial and complex impact on nutritional status. Firstly, heavy alcohol consumption can significantly reduce dietary intake. Secondly, the metabolism of ethanol involves energy-wasting pathways. Thirdly, chronic alcohol consumption can result in the wastage of fat and muscle. Fourth, many alcohol-related diseases can interfere with dietary intake and contribute to malnutrition, such as chronic alcoholic gastritis, chronic pancreatitis, and chronic liver disease. Finally, alcohol decreases muscle protein synthesis via inhibition of mTOR-dependent translation initiation . All studies included in this systematic review considered active alcohol abuse as an exclusion criterium for patient enrollment; therefore, we should not consider alcohol consumption as an active player in the nutritional modifications reported in these studies.

The indications for TIPS insertion were refractory ascites and variceal bleeding, the most commonly used stent material in the studies was polytetrafluoroethylene, and the post-TIPS portal pressure gradients ranged from 6.0 to 15.5 mmHg. Although the patient populations might have overlapped in some studies, we decided to include these studies because they provided unique information, such as a specific measure of nutritional status or a different time point since TIPS insertion.

The results of the qualitative analysis showed marked improvements in muscle mass and a shift in fat tissue distribution after TIPS placement. There are several

potential explanations for the observed changes in body composition after TIPS placement. These changes may be related to the reduction in portal hypertension [8] and its associated effects on gut permeability, bacterial translocation, proinflammatory cytokines, and chronic inflammation. Additionally, the TIPS procedure may improve protein-losing enteropathy and reduce frequent hospitalizations due to gastrointestinal bleeding and paracentesis, leading to improved mobility and oral intake. Unfortunately, only limited information was available regarding dietary changes after TIPS. In a study by Tsien et al., only 25% of patients reported an increase in their total dietary intake[190].

It is worth noting the relationship between the nutritional status before TIPS and the reported nutritional improvement after the procedure. Two studies found that the improvement in nutritional status was more pronounced in patients with sarcopenia or who were underweight or of normal weight, rather than in overweight or non-sarcopenic individuals. Liu et al. found an increase in SMA, SMI, SFA, and SFT in sarcopenic patients, while they did not observe any significant change in non-sarcopenic patients. Montomoli et al. found an increase in dry lean mass in the group of normal or underweight patients but not in the group of overweight patients. Tsien et al. also reported that younger age, male sex, and lower pre-TIPS muscle area were independent predictors of increased muscle mass after TIPS [190].

These findings create a sort of paradox, as malnutrition and sarcopenia have been associated with increased risk of adverse outcomes after TIPS placement, namely, hepatic encephalopathy, acute on chronic liver failure, or mortality. This was the reason why the latest Baveno VII consensus discouraged sarcopenia itself as an indication for TIPS insertion, though these patients are likely to benefit the most from TIPS in terms of nutritional improvement. When considering an elective TIPS procedure for a malnourished sarcopenic patient, clinical judgment must account for two factors: the short-term risks of the procedure and the potential long-term benefits—correcting portal hypertension and improving the patient's nutritional status.

Several studies have also observed alterations in adipose tissue composition following TIPS placement. Significant expansion of subcutaneous fat tissue was observed in all studies[166], with the exception of one study. Additionally, a notable reduction in visceral fat tissue was reported in two studies, while remaining unchanged in one study[190]. There is evidence to suggest that the procedure leads to a

decrease in VAT and an increase in SAT. The venous drainage of VAT occurs directly via the portal circulation to the liver. Therefore, changes in portal circulation subsequent to TIPS placement may enhance the availability of these fat deposits to be metabolized as energy sources by the liver. Additionally, increased circulating levels of adipokines have been observed post-TIPS placement, potentially reflecting anabolic changes that contribute to the alterations in adipose tissue observed in patients undergoing TIPS.

The considerable clinical and methodological heterogeneity between studies precluded the conduct of a quantitative analysis (meta-analysis). The variability in nutritional status evaluation across studies was identified as a major contributing factor to this limitation. Indeed, the methods used to evaluate nutritional status varied widely across studies, including the use of Body Mass Index (BMI), weight, body cell mass, skeletal muscle volume and function, and measures of adipose tissue. Furthermore, the time interval between TIPS placement and nutritional reassessment ranged from 1–3 to 19 months. Shorter follow-up times might have limited the observation of significant changes, while longer follow-up times may have resulted in significant selection bias, as patients who had died or undergone transplantation were more likely to be excluded from the analysis.

Finally, it is crucial to conduct well-designed prospective studies using gold-standard methods for evaluating malnutrition, in order to identify patients who would most benefit from TIPS placement, including from a nutritional perspective. These efforts could provide not only new pathophysiological insights into the relationship between portal hypertension and malnutrition, but could also answer the question of the optimal timing for TIPS insertion in sarcopenic cirrhotic patients.

In conclusion, the results of this review indicate an improvement in ascites-free weight and body mass index following the TIPS procedure. This improvement has been associated with an increase in muscle mass, as evidenced by various measures such as the skeletal muscle index or skeletal muscle area. Additionally, TIPS placement leads to a redistribution of fat mass, with a preference for subcutaneous over visceral adipose tissue. Sarcopenic patients seem to benefit the most from TIPS placement in terms of nutritional status.

STUDY 3 - *Prognostic Impact and Assessment of Nutritional Changes in Patients with Liver Cirrhosis Undergoing Transjugular Intrahepatic Portosystemic Shunt (TIPS): A Prospective Study*

S3.1 RATIONALE

From the previous systematic review the longitudinal changes of body composition after TIPS and the evidence of a prognostic value of baseline body composition before TIPS are scarce, mainly based on retrospective, monocentric studies with small sample size with high variability in study design and muscle mass measurements[175].

In order to provide solid evidence on this topic, we have designed a multicenter prospective study with baseline and repeated CT-scan as the gold standard for the evaluation of muscle mass and quality and of adiposity.

S3.2 METHODS

This was a multicenter, prospective study designed to assess the prognostic value of muscle alterations and adiposity at baseline in predicting post-TIPS HE. Secondary objectives included a longitudinal evaluation of changes in muscle mass, muscle quality, and adiposity after TIPS, and the assessment of whether improvement in body composition was associated with a reduced risk of post-TIPS HE. HE was chosen as a clinical end point as it was previously reported that HE after the TIPS procedure may be influenced by muscle tissue .

Patient Population. All patients aged 18 years or older with cirrhosis who underwent TIPS placement for standard clinical indications were consecutively enrolled between March 2021 and March 2025 at five Italian centers: Policlinico Umberto 1- Sapienza University of Rome, University Hospital of Modena, Ospedale Santa Maria Goretti of Latina, ISMETT IRCCS Palermo, and Azienda Ospedaliera Santa Maria of Terni. Eligible patients were required to have a clinical and/or histological diagnosis of cirrhosis, a clear indication for TIPS placement according to the Baveno VII consensus, and an available contrast-enhanced CT scan performed close before the procedure (range 0-3 months).

Patients were excluded if they had hepatocellular carcinoma beyond the Milan criteria, non-cirrhotic portal hypertension, or a history of liver transplantation (LT). Individuals enrolled in clinical trials including nutritional support in the context of TIPS procedures were also excluded. All other exclusion criteria aligned with those recommended for TIPS eligibility according to the contemporaneous Baveno VII guidelines[197].

Data Collection. At baseline, demographic and anthropometric characteristics were recorded, together with a comprehensive clinical evaluation that included history of liver decompensation, etiology of cirrhosis, relevant comorbidities, concomitant medical therapies, and information on active alcohol use and possible withdrawal after TIPS. Laboratory analyses comprised hemogram, AST, ALT, GGT, alkaline phosphatase, albumin, creatinine, bilirubin, sodium, and INR, and were collected both at baseline and after six months. From these data, Child-Pugh and MELD scores were calculated at both time points. The clinical assessment included grading of ascites according to the International Club of Ascites, evaluation of gastroesophageal varices based on AASLD classification, and a history of previous episodes of overt hepatic encephalopathy scored using the West Haven criteria. The occurrence of acute-on-chronic liver failure (ACLF), infections, and acute kidney injury (AKI) was reported both at enrollment and within six months after TIPS. Hemodynamic parameters such as stent diameter and portal pressure gradient were measured before and after TIPS placement, with portal pressure recorded in the portal trunk and systemic venous pressure in the inferior vena cava at the stent exit[198].

Patients were followed for twelve months after TIPS, with at least one scheduled visit within six months of the procedure and additional visits when clinically indicated. Outcomes of interest included: incidence of HE, overall mortality, hospitalizations for any cause, LT, TIPS failure, liver-related complications (infections, AKI, ACLF). TIPS failure was defined as the need for large-volume paracentesis (LVPs) for ascites recurrence three months or more after the procedure, the occurrence of variceal rebleeding, or the need for TIPS revision, with stent dilatation. The occurrence of HE during follow-up was classified according to the West Haven criteria. Family members and/or caregivers were instructed to promptly recognize the early signs of HE and contact the referral center for clinical

assessment. The study protocol was approved by the Ethics Committee of Sapienza University of Rome, acting as the coordinating center (EC Prot. 0560/2022).

TIPS Procedure. TIPS placement was performed by experienced interventional radiologists under general anesthesia with remifentanil and midazolam. Vascular access was obtained through the right internal jugular vein, followed by catheterization of a hepatic vein under fluoroscopic guidance. A curved needle was then advanced through the liver parenchyma to reach the portal vein. All patients received a new-generation VIATORR endoprosthesis (Gore). The choice of stent diameter followed local policies, and underdilatation was permitted when clinically appropriate. Portocaval pressure gradient was measured at the time of portal vein puncture and again after stent deployment. The definition of adequate hemodynamic response to TIPS was not standardized and varied slightly across centers.

Muscle and adipose tissue assessment. CT scans at the L3–L4 level were employed as the gold standard for the assessment of muscle mass, muscle quality, and adipose tissue [5]. All CT images were centralized in DICOM format at the coordinating center (Policlinico Umberto I, Rome) and analyzed by two expert evaluators (S.D.C. and L.L.) using SliceOmatic software, version 5.0 (TomoVision, Montreal, Canada).

Skeletal muscle mass was identified within the attenuation range of –29 to +150 Hounsfield units (HU). The cross-sectional muscle area was normalized to height squared, yielding the Skeletal Muscle Index (SMI). Sarcopenia was diagnosed when SMI values were <50 cm^2/m^2 in men and <39 cm^2/m^2 in women[124]. Improvement in muscle mass was defined as either the reversion of sarcopenia at the follow-up CT scan or a relative increase of at least 5% compared with baseline values.

Muscle quality was assessed indirectly through mean muscle attenuation (HU). Patients were classified as having myosteatosis when mean muscle attenuation was <41 HU in individuals with a BMI <24.9 kg/m^2, or <33 HU in those with a BMI ≥25 kg/m^2 [132].

Visceral adipose tissue (VAT) was defined within the range of –150 to –50 HU (PMID: 8782734), while subcutaneous adipose tissue (SAT) was defined between –190 and –30 HU (PMID: 3710689). SAT radiodensity (RSAT) was determined as the mean attenuation value of SAT. High RSAT (HRSAT) was defined as a mean

SAT attenuation above –83 HU in women and above –74 HU in men, according to previously published thresholds[91].

Statistical analysis. Continuous variables are presented as medians with interquartile ranges (IQR) and compared between groups using the Mann–Whitney U test or Wilcoxon signed-rank test for paired analyses. Categorical variables are reported as absolute numbers and percentages, with differences assessed by the χ^2 test or Fisher's exact test as appropriate. Survival analyses were performed using Kaplan–Meier estimates and compared by log-rank testing. To identify predictors of post-TIPS HE, univariable and multivariable Cox proportional hazards models were constructed. In multivariable models, age, MELD score, and history of HE were included as covariates, and nutritional parameters were introduced one at a time to avoid overfitting given the limited number of events. Hazard ratios (HR) with 95% confidence intervals (CI) were reported. Statistical significance was defined as a two-tailed $p < 0.05$. Analyses were conducted using R (version 4.5.1).

S3.3 Results.

Patient characteristics. A total of 85 patients with cirrhosis undergoing TIPS were enrolled. An additional 112 patients were assessed but excluded from the study, primarily due to the absence of an available CT scan within the required time frame (60 patients) or refusal to participate in the study protocol (32 patients). Other reasons for exclusion included emergency TIPS placement (15 patients) and various other criteria. Median age was 59 years (IQR 54–66), and 63 (74.1%) were male. The most common indication for TIPS was refractory ascites (43, 50.5%), followed by failure of secondary prophylaxis for variceal bleeding (23, 27%). Alcohol-related cirrhosis accounted for 60% of cases, whereas metabolic etiology was present in 31.7%. Pre-TIPS HE was reported in 25 patients (29.4%). Median MELD and Child-Pugh scores at baseline were 11 (IQR 9–14) and 7 (IQR 6–8), respectively. Additional clinical and biochemical features are reported in Table 5.

Therapy with lactulose and/or rifaximin was administered to 59 patients (72%), either as treatment for a prior episode of HE or as prophylaxis against post-TIPS HE. Specifically, rifaximin was used in 44 patients (51.7%) before TIPS placement.

During the 6-month follow-up after TIPS, 35 patients (41.2%) developed HE, of which 32 were overt (grade >2) with a median time of 1.23 months (95% CI, 0.7-2.4). ACLF occurred in 6 patients (7%), while infections and AKI were observed in 22 (25.8%) and 8 (9.5%) patients, respectively. Ascites was present in 24 patients (28.2%), but only 9 required LVP. TIPS failure was documented in 13 patients (15.3%). At 12 months, 9 patients (10.6%) had died, 9 had undergone transplantation, and 42 (49.4%) required hospitalization after TIPS.

Baseline body composition. Median SMI at baseline was 47 cm²/m² (IQR 39–54), with sarcopenia present in 47 patients (55%). Myosteatosis was highly prevalent (69 patients, 81%), with a median muscle attenuation of 30 HU (IQR 26–37). The combined presence of sarcopenia and myosteatosis was observed in 41 patients (48%). Median VAT and SAT areas were 105 cm² (IQR 65–194) and 130 cm² (IQR 75–235), respectively, with a median VAT/SAT ratio of 0.92 (IQR 0.58–1.28). Median RSAT was –90 HU (IQR –97 to –78), and 20 patients (24%) were classified as having HRSAT.

Nutritional predictors of post-TIPS outcome. Patients who developed HE after TIPS showed a non-significant trend toward lower SMI compared with those without HE (44, 95% CI 38–55 vs. 48, 95% CI 39–51; p=0.5). The prevalence of sarcopenia was slightly higher in the HE group than in patients without HE (57% vs. 54%; p=0.8). Similarly, no significant differences were observed between groups in the distribution of myosteatosis, the coexistence of sarcopenia and myosteatosis, or changes in adipose tissue (Table 7). These findings were consistent even when restricting the analysis to patients with HE $\geq$ grade 2.

Multivariable Cox regression models for the risk of postTIPS HE were fitted including age, MELD, history of HE, and one nutritional variable at a time. No significant correlations with HE were found in muscle and adipose tissue variables. Analysis restricted to patients undergoing TIPS for refractory ascites (n=43; 21 with HE) yielded similar results.

At baseline, no biochemical differences were detected between groups; however, at 6 months, patients with HE had lower hemoglobin levels, reduced GGT, and higher MELD and Child-Pugh score compared with those without HE.

Regarding adipose tissue parameters, higher RSAT (-92 HU Vs -78 HU, p 0.030) and increasing in the prevalence of HRSAT (15% Vs 46%, p 0.002) appear to be related with post-TIPS ascites, together with the reduction in SAT and VAT values.

Moreover, RSAT and the prevalence of HRSAT were higher (-92 HU Vs -72 HU, p 0.04 and 17% Vs 54%, p 0.008 respectively) in patients with diagnosis of TIPS failure. Lastly, increased VAT/SAT ratio at the repeated CT-scan was associated with 12-months mortality (0.83 Vs 1.23, p 0.038).
Neither the indication for TIPS placement, stent diameter, nor hemodynamic parameters at the time of TIPS insertion influenced the incidence of post-TIPS HE (Table 6).

Longitudinal changes after TIPS and clinical implications. Of the original cohort of 85 patients, 60 (70.5%) underwent a repeated CT scan at 6 ± 3 months, with a mean interval of 5.6 months (SD 2.6). The main reasons for missing follow-up imaging were patient refusal or loss to follow-up (18 patients), followed by death (5 patients) or liver transplantation (2 patients) before the 6-month assessment.

Among the 60 patients with repeated CT evaluation, 33 (55%) were diagnosed with sarcopenia at baseline, whereas 27 (38.3%) had sarcopenia at 6 months. The mean SMI significantly increased after TIPS (47.31 ± 11.13 vs. 49.91 ± 10.84, p=0.001).

Muscle attenuation remained stable after TIPS (31.27 ± 7.63 HU vs. 31.88 ± 7.80 HU, p=0.289), and the prevalence of myosteatosis was similar at baseline and follow-up (47 patients, 78.3% vs. 42 patients, 70%).

Regarding adipose tissue, a significant reduction in VAT area was observed (143.22 ± 100.75 cm² vs. 102.38 ± 70.32 cm², p<0.001), while SAT showed a nonsignificant trend toward increase (167.51 ± 111.37 cm² vs. 174.47 ± 108.81 cm², p=0.096). Consequently, the VAT/SAT ratio improved after TIPS (0.98 ± 0.57 vs. 1.02 ± 2.32, p<0.000). Finally, RSAT values did not show significant changes after TIPS (−87.64 ± 18.05 HU vs. −83.93 ± 27.63 HU, p=0.471).

We explored the clinical implication of changes in body composition after TIPS. We found a relevant trend in reduction of muscle mass (152 cm^2 Vs 129 cm^2, p 0.078) and muscle attenuation (32 HU Vs 29 HU, p value 0.068) in patients with post TIPS HE. The latter also showed nonsignificant higher prevalence of sarcopenia and myosteatosis (50% Vs 41% and 78% Vs 68% respectively).

Analysis of post-TIPS HE, accounting for baseline status and longitudinal changes, showed that patients with sarcopenia at enrollment who did not experience reversion

had a higher risk of OHE (12/23 patients, 52%) compared with those who either recovered from sarcopenia or had no baseline sarcopenia (33%). This difference did not reach statistical significance, most likely due to the limited sample size.

The prevalence of patients with HRSAT was consistently higher in the HE group (10 patients, 36%) compared with the non-HE group (3 patients, 9.4%, p 0.013), while no differences were observed in other adipose tissue variable distributions in the two groups (Table 7).

S3.4 Discussion. Our prospective multicenter study investigated the role of body composition in the clinical outcomes of patients with cirrhosis undergoing TIPS placement, with a longitudinal assessment of nutritional changes and their prognostic implications. The prevalence of sarcopenia (55%) and myosteatosis (approximately 80%) in our cohort was consistent with previous reports in patients with advanced cirrhosis and complications of portal hypertension. Similarly, the distribution of adipose tissue showed a predominance of visceral adipose tissue (VAT) compared with subcutaneous adipose tissue (SAT), resulting in an unfavorable VAT/SAT ratio, a typical feature of chronic proinflammatory systemic conditions. SAT radiointensity was -90 HU, very similar to the -87 HU reported by Ebadi et al [91]., with a prevalence of patients with high RSAT of 20% (compared with 25% in their cohort of cirrhotic patients awaiting liver transplantation).

We were unable to demonstrate a significant association between loss of muscle mass and post-TIPS HE, as previously reported in the literature[158]. Although there was a trend toward a greater reduction in SMI and a higher prevalence of sarcopenia among patients who developed HE, these findings did not reach statistical significance. A recent systematic review of 22 studies, though limited by marked heterogeneity, concluded that malnutrition and sarcopenia were associated with worse outcomes after TIPS, particularly with increased incidence of HE[199]. The rationale for this association is that skeletal muscle contributes to ammonia detoxification by converting ammonia into glutamine, subsequently excreted by the kidneys[39]. Consequently, muscle wasting and impaired anabolic capacity are strongly linked to higher HE risk[200]. On the other hand, TIPS has been shown to improve muscle mass in some studies, although the available evidence is weak due to lack of standardization and poor study quality, as we highlighted in our previous systematic review. Muscle gain following TIPS may mitigate the effect of baseline sarcopenia

on the development of post-TIPS HE, particularly in prospective studies specifically designed to assess nutritional status and less prone to the selection bias inherent to retrospective designs. In our multivariate analysis, adjusted for known competing factors, no significant association was found between nutritional parameters and post-TIPS HE. Sub-analyses restricted to patients undergoing TIPS for refractory ascites yielded similar results. Moreover, neither hemodynamic parameters nor TIPS stent diameter correlated with HE occurrence. Interestingly, prophylactic therapy with lactulose and rifaximin was more frequently prescribed in patients who developed post-TIPS HE, likely reflecting their use in individuals considered at higher baseline risk. This difference was statistically significant only for lactulose, whereas rifaximin use was similar between groups and showed no relevant protective effect.

TIPS placement was associated with favorable changes in body composition, likely mediated by improvements in portal hypertension, reductions in hospitalizations, and attenuation of systemic inflammation. However, the available evidence remains scarce and generally of low quality. Our study represents the first multicenter prospective evaluation of longitudinal body composition changes after TIPS, based on repeated CT scans at 6 months. Hey et al. previously reported the only prospective longitudinal study on this topic, but their cohort included only twelve patients[201]. In our cohort of sixty patients with repeated CT scans, consistent beneficial effects of TIPS were observed. Specifically, we documented a significant increase in SMI, a reduction in VAT, and a trend toward increased SAT, resulting in a significantly improved VAT/SAT ratio, indicative of a more favorable anti-inflammatory profile. Mean muscle attenuation (reflecting myosteatosis) remained stable after TIPS, as did SAT radiointensity, which we describe here for the first time in this clinical setting. Consequently, the prevalence of sarcopenia decreased from 55% to 38.3%, while myosteatosis prevalence remained stable (78.7% vs. 70%). Accordingly, the prevalence of combined sarco-myosteatosis declined from 48.3% at baseline to 38.8% at follow-up. These changes were reflected in reversion of sarcopenia in 6 patients (10%) and muscle gain in 36 patients (60%).

Some evidence suggests that improvements in body composition may translate into better clinical outcomes after TIPS. In our cohort, no significant differences in

muscle mass, muscle quality, or adipose tissue distribution were found between patients with and without post-TIPS HE, except for a significantly higher proportion of patients with high RSAT in the HE group. PThe prognostic role of RSAT has been demonstrated in several other settings [202,203], where it has been linked to a pro-inflammatory profile. Ebadi et al. provided histological evidence that patients with high RSAT levels present smaller adipocytes, expanded interstitial space, and mononuclear cell infiltration; these features indicate structural alterations of adipose tissue that may reflect underlying inflammatory processes[91]. In our cohort, RSAT showed a strong association with post-TIPS ascites and TIPS failure, suggesting a potential role of an altered pro-inflammatory profile in determining procedural outcomes. Moreover, an increased VAT/SAT ratio at follow-up CT scan was associated with 12-month mortality after TIPS. To our knowledge, this is the first report describing the prognostic role of RSAT and VAT/SAT ratio in the TIPS setting, which appear to be more relevant than changes in muscle mass or muscle quality, and should be further validated in larger prospective studies.

Nevertheless, in the context of generalized improvements in muscle mass after TIPS observed in the majority of patients (which may buffer hyperammonemia due to shunt creation), the absence of SMI improvement itself may represent a potential risk factor for post-TIPS HE. Similarly, we observed a trend toward higher incidence of overt HE in patients with baseline sarcopenia who did not experience reversion, compared with those who either recovered from sarcopenia or had no baseline sarcopenia. These findings warrant confirmation in larger cohorts with higher event rates, ideally within specifically designed clinical studies focusing on the prognostic relevance of muscle mass improvement (or lack thereof) after TIPS.

To our knowledge, this is the first multicenter prospective study investigating the role of body composition in predicting post-TIPS events. Moreover, it is the largest study to longitudinally evaluate changes in body composition after TIPS and their clinical implications. Our study is also the first to provide a comprehensive analysis of adipose tissue in the TIPS setting, including novel and promising parameters such as the VAT/SAT ratio and the radiointensity of SAT. Additionally, our dataset includes detailed patient histories, medical therapies, and hemodynamic parameters. Limitations of the study include the small number of events, which restricts the ability to perform integrated multivariable analyses accounting for all competing risk

factors. Other limitations include the lack of standardization in the diagnosis of minimal hepatic encephalopathy (mHE) across different centres and the use of general anesthesia during TIPS placement, which may have affected hemodynamic parameters.

In conclusion, our prospective multicenter study demonstrated that TIPS placement was associated with favorable changes in body composition. The prognostic role of muscle mass in predicting post-TIPS outcomes should, however, be reconsidered and interpreted in relation to baseline sarcopenia and, more importantly, to the absence of muscle gain, which likely represents the principal driver of increased post-TIPS complications, particularly HE. Conversely, patients who experienced muscle gain appeared to be protected against the risk of post-TIPS HE. Finally, adipose tissue parameters should also be regarded as clinically relevant in the stratification of post-TIPS outcomes.

FIGURES

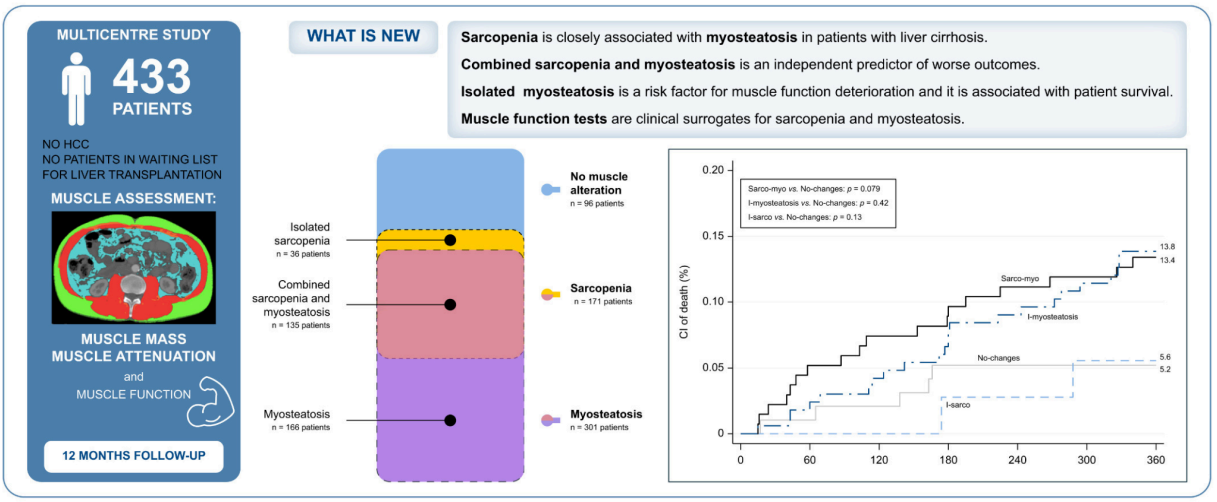
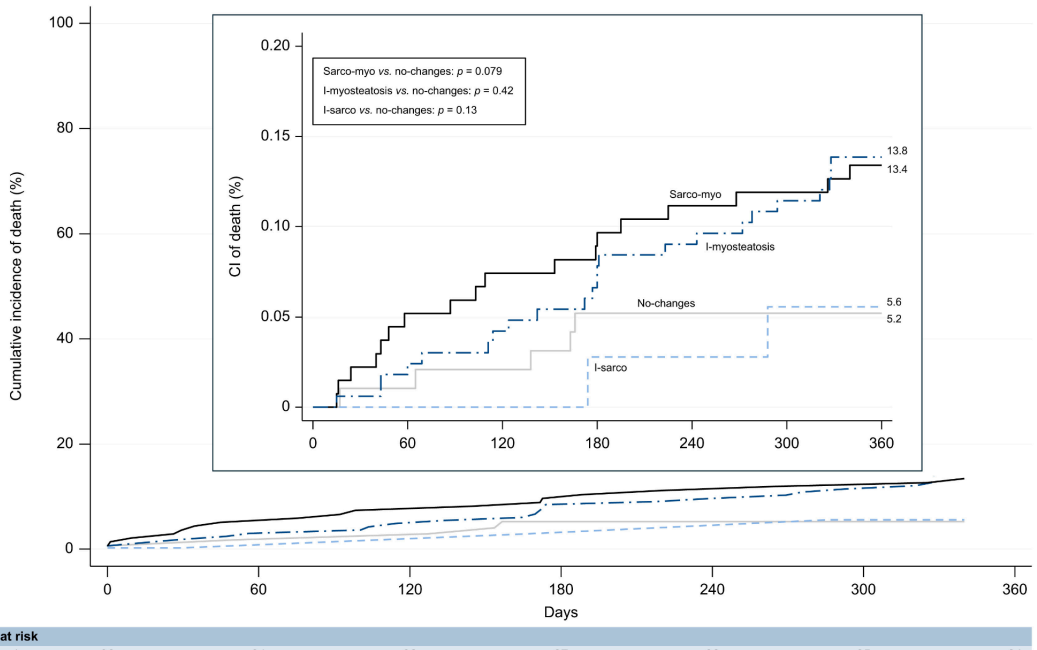
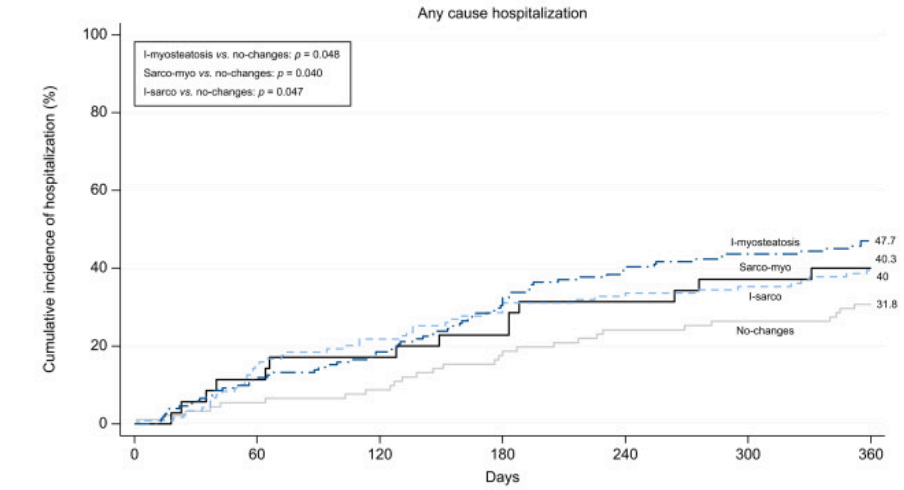


Fig 1. Graphical abstract of the multicenter EpatoSarco study, summarizing the main finding of the manuscript



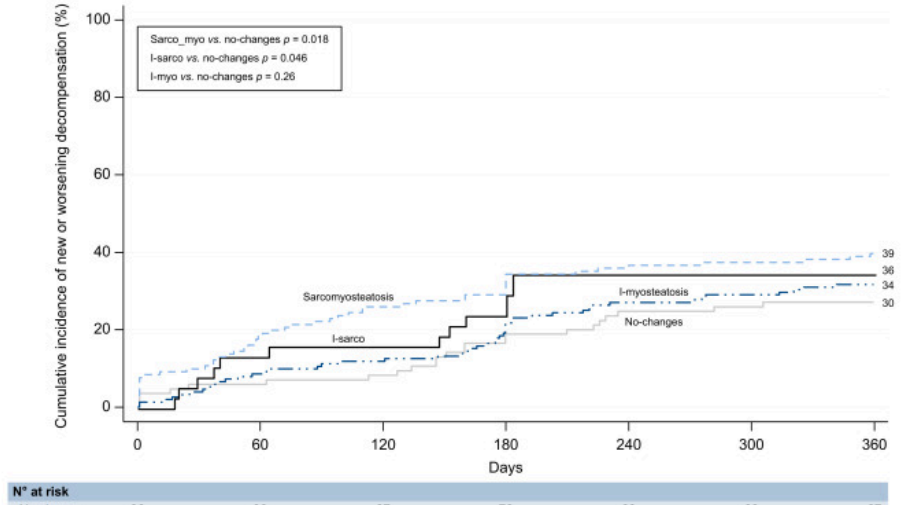
N° at risk							
No changes	96	94	92	87	86	85	84
I-sarco	36	34	33	30	29	28	26
Sarco-myo	135	123	117	112	107	105	103
I-myosteatosis	166	163	158	152	146	140	133

Fig. 2 Cumulative incidence of death with liver transplantation as a competing risk in four patient subgroups according to the type of muscle damage.



N° at risk							
No changes	96	87	83	73	67	65	61
I-sarco	36	29	26	22	18	16	15
Sarco-myo	135	95	85	74	67	64	59
I-myosteatosis	166	140	129	108	89	82	75

Fig. 3 Cumulative incidence of hospitalization, with death and liver transplantation as competing risks, in four patient subgroups according to type of muscle damage.



N° at risk							
No changes	96	90	87	76	69	68	67
I-sarco	36	29	27	23	18	17	17
Sarco-myo	135	103	91	84	74	72	68
I-myosteatosis	166	153	146	130	114	108	100

Fig. 4 Cumulative incidence of new liver decompensation (first or further) with death and liver transplantation as competing risks in four patient subgroups according to type of muscle damage.

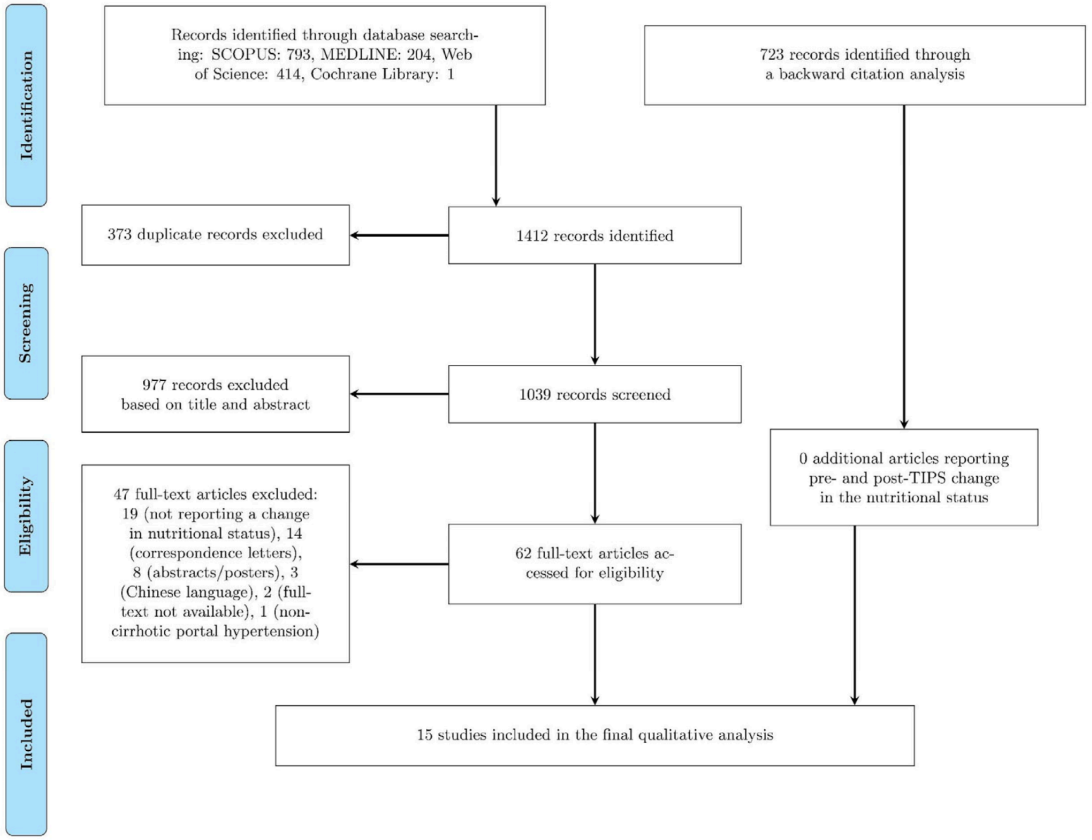


Figure 5. Flow of information through different phases of the systematic review.

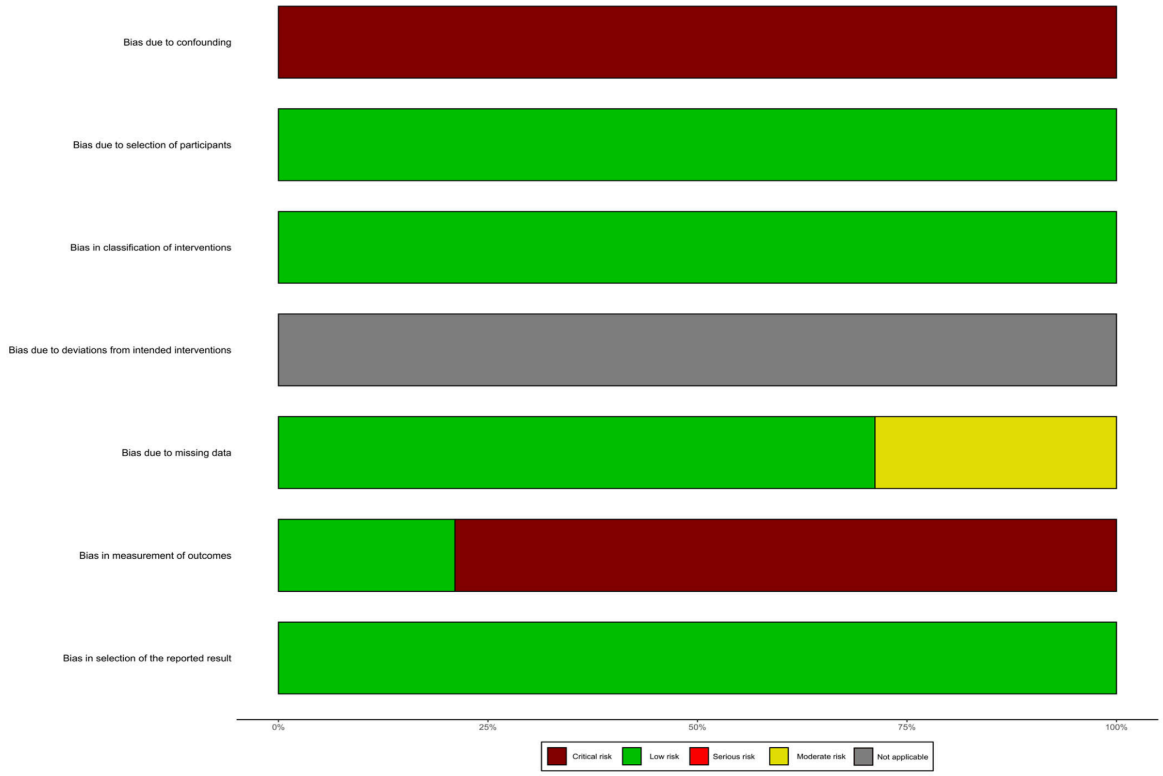


Figure 6. Risk of bias assessment according to the ROBINS-I guidelines (Risk of Bias in Non-randomized Studies of Interventions).

TABLES.

Table 1. Patient characteristics at inclusion and major clinical outcomes*

	Whole cohort*	No muscle changes	I-Sarco [¶]	I-Myo [¶]	Combined Sarco-Myo [¶]
Patients	433	96 (22.2)	36 (8.3)	166 (38.3)	135 (31.1)
Age, yrs	57.1 (8.9)	56.7(8.9)	58.6 (9.2)	60.8 (8.7) [0.0003]	60.7 (9.0) [0.0009]
Sex M	308 (71.1)	82 (85.4)	31 (86.1)	101 (60.8) [<0.0001]	94 (69.6) [0.005]
Etiology					
Alcohol	173 (39.9)	37(38.5)	10 (27.7)	67 (40.4)	59 (43.7)
HCV	67 (15.5)	18(18.8)	10 (27.7)	22 (13.2)	17 (12.6)
HBV	19 (4.4)	7 (7.3)	0	6 (3.6)	6 (4.4)
Alcohol+virus	38 (8.8)	12(12.5)	1 (2.8)	12 (7.2)	13 (9.6)
NASH	65 (15.0)	12 (12.5)	8 (22.2)	31 (18.7)	14 (10.4)
Autoimmune/Biliary disease	9 (2.1)	0	2 (5.6)	4 (2.4)	3 (2.2)
Others or undefined	62 (14.3)	10 (10.4)	5 (13.9)	24 (14.5)	23 (17.0)
Metabolic					
BMI	19.2(10.1)	18.7(11.5)	21.9(7.0)	17.5(11.19)	20.9(7.6)
Diabetes	138 (31.9)	33 (34.4)	8 (22.2)	61 (36.7)	36 (26.7)
Hypertension	160 (36.9)	30 (31.3)	10 (27.8)	72 (43.4) [0.05]	48 (35.6)
Dyslipidemia	75 (17.3)	17 (17.7)	5 (13.9)	36 (21.7)	17 (12.6)
Laboratory/ Clinical					
INR	1.4(0.38)	1.34(0.23)	1.34(0.27)	1.43(0.41) [0.036]	1.42(0.41)
Albumin, g/L	35.8(0.72)	37.4 (7.91)	37.7(7.51	35.7(7.0)	3.43 [0.0015]
Bilirubin, mg/dL	2.9 (4.5)	2.3 (2.4)	2.6 (4.0)	2.5 (3.0)	3.9 (6.7) [0.02]
Creatinine, mg/dl	0.90(0.53)	0.88(0.36)	0.83(0.18)	0.87(0.32)	0.97
Hb, g/dl	11.9(2.4)	12.5(2.3)	12.0(2.4)	11.9(2.3) [0.05]	11.3 [0.0001]
E-G Varices╫	277 (64.4)	68 (71.6)	23 (63.9)	105 (64.0)	81 (60)
Ascites	215 (49.7)	35 (36.5)	19 (52.8)	72 (43.4)	89 (65.9) [<0.0001]
Hepatic encephalopathy	86 (19.9)	17 (17.7)	10 (27.8)	36 (21.7)	23 (17.0)
ANT [n=348]╪	17.1 (6.18)	18.4 (5.3)	18.8 (6.1)	16.2 (6.2) [0.01]	16.8 (6.5) [0.03]
Child-Pugh	7.5 (2.0)	7.0 (1.78)	7.2 (1.9)	7.4 (2.1)	7.9 (2.0) [0.0009]
A ┤	162 (37.4)	44(45.8)	12(33.3)	68 (41.0)	38 (28) [0.018]
B ┤	196 (45.3)	40 (41.7)	18 (50)	68 (41.0)	70 (51.9) [0.018]
C ┤	75 (17.3)	12 (12.5)	6 (16.7)	30 (18.0)	27 (20) [0.018]
MELD score	12.9 (4.9)	12.2 (3.9)	11.6 (5.2)	12.9 (4.8)	13.9 (5.5) [0.007]
MELD-Na score	14.3 (5.4)	13.2 (4.3)	12.5 (6.3)	14.3 (5.2)	15.6 (5.9) [<0.001]
Ongoing Therapies					
I-Prophylaxis ├	221 (51)	52 (54.2)	22 (61.1)	79 (47.6)	68 (50.4)
NSBB	109 (25.2)	24 (25)	12 (33.3)	41 (24.7)	32 (23.7)
EVL	41 (9.5)	11 (11.5)	2 (5.6)	15 (9.0)	13 (9.6)
II-Prophylaxis §	71 (16.4)	17 (17.7)	8 (22.2)	23 (13.9)	23 (17.0)
Rifaximin	99 (24.5)	26 (27.7)	10 (31.2)	40 (26.0)	23 (18.6)
Lactulose	181 (44.8)	44 (46.8)	16 (50)	73 (47.4)	48 (38.7)
Albumin	59 (14.6)	15 (15.9)	4 (12.5)	24 (15.6)	16 (12.9)
Outcome events, N (Incidence rate per 100 patient-years)					
Follow-up, p-yrs #	414	95	36	158	125
Death	51 (12.3)	5 (5.2)	2 (5.6)	24(15.2) [0.015]	20(16.0) [0.012]

Liver transplant	42 (9.7)	10(10.5)	8(22)	10 (6.3)	14(11.2)
New Hospitalization	207 (50.0)	33 (34.7)	17 (47.2)	88 (55.7) [0.0012]	69 (55.2) [0.0025]
All decompensation	143(31.4)	24 (25.3)	11 (30.6)	45 (28.5)	50 (40.0) [0.023]

*Data are presented as number of patients or means and % or SD in brackets, as appropriate
p value for significant differences from patients without muscle changes
╫ Esophago-Gastric varices
╪ANT= animal naming test, available in 348 patients
╞ Primary prophylaxis for variceal bleeding
§ Secondary prophylaxis for variceal bleeding, mostly NSBB+EVL
┤Child-Pugh class A, B, C.
patient years
Abbreviations: MELD, model for end stage liver disease; NSBB, non-selective beta blockers; EVL, endoscopic variceal ligation;

Table 2. Functional tests and CT parameters of the whole population and of subgroups of patients according to the type of muscle changes

Parameter	**Whole cohort**	**No muscle changes**	**I-Sarco [¶]**	**I-Myo [¶]**	**Combined Sarco-Myo [¶]**
Functional tests, mean (SD)					
Frailty liver index (N=238)*	3.77(0.85)	3.49(0.82)	3.50(0.60)	3.83(0.88) [0.021]	3.96(0.84) [0.0022]
Hand grip, Kg (N=263)*	33.87(16.3)	38.26(17.33)	31.99(8.88)	34.78(17.03)	29.71(15.17) [0.0021]
Up & go test, sec (N=226)*	11.8(5.4)	9.9(3.9)	8.0(2.9)	13.3(5.7) [0.0002]	12.6(5.5) [0.003]
Computed tomography parameters, mean (SD)					
N patients	433	96	36	166	135
L3 SMI ǂ	50.3(10.9)	59.1(8.8)	43.4(5.3) [<0.0001]	54.2(9.4) [<0.0001]	41.2(6.6) [<0.0001]
Muscle attenuation,%HU	31.6(8.4)	39.8(5.1)	40.1(6.0)	27.8(6.8) [<0.0001]	28.2(6.7) [<0.0001]
Visceral adipose tissue	150.8(91.8)	158.5(87.7)	111.6(80.7) [0.006]	170.2(100.1)	131.9(79.8) [0.017]
S-C adipose tissue ╞	196.8(120.6)	213.5(106.7)	137.5(89.5) [0.0002]	236.1(132.9)	152.8(99.9) [<0.0001]

p value for significant differences compared with patients without muscle changes
*Number of patients with available information
ǂL3 skeletal muscle index
╞ SAT subcutaneous adipose tissue
HU, Hounsfield unit.

Table 3. Significant risk predictors for death, hospitalization and new decompensation by the Fine and Gray model, and including MELD and Child-Pugh score.

Variable	Score	Sub-Hazard Ratio	p	95% Confidence Interval	
Including MELD and excluding relevant single components					
Death (LT competing)					
Muscle changes	No=0; I-sarco=1, I-myo =2; sarco-myo=3	1.36	**0.058**	0.99	1.86
MELD	Continuous values	1.12	<0.0001	1.06	1.86
HE	No=0; yes=1	2.09	0.011	1.18	3.69
Ascites	No=0; yes=1	2.73	0.005	1.35	5.52
Hospitalization (death and LT competing)					
Muscle changes	No=0; I-sarco=1, I-myo =2; sarco-myo	1.18	**0.012**	1.04	1.35
MELD	Continuous values	1.36	0.191	0.99	1.06
Albumin	g/L	1.28	0.052	0.998	1.65
Ascites	No=0; yes=1	1.86	0.062	0.98	1.91
First or further decompensation (death and LT competing)					
Muscle changes	No=0; I-sarco=1, I-myo =2; sarco-mio=3	1.04	0.60	0.90	1.20
MELD	Continuous values	1.04	0.02	1.01	1.07
Ascites	No=0; yes=1	2.49	<0.0001	1.72	3.62
HE	No=0; yes=1	1.48	0.038	1.02	2.15

In these analyses, each of the assessed muscle changes (i.e I-sarcopenia, I-myosteatosis, sarco-myosteatosis) were scored as absent/present: when none of them was significant, we included in the model a discrete variable scored as follows: no-changes=0, isolated sarcopenia=1, isolated myosteatosis=2, sarcopenia and myosteatosis=3.

Table 4. Main changes in the nutritional status after transjugular intrahepatic portosystemic shunt placement in cirrhotic patients.

Reference	Design	Sample Size	TIPS Indication	Follow-Up after	Measure	Change
Allard et al. (2001)	-	14 (71% ♂)	RA (100%)	12 M	W, Dry W, FM, F10/F30, and MRR	Significant increase in Dry W and FM.
Artru et al. (2020)	RS	179 (72% ♂)	RA (47.5%), VB (52.5%)	6 M	TPMT, TPMA, SFA, and VFA	Significant increase in TPMT, TPMA, and SFA and significant decrease in VFA.
Gioia et al. (2019)	RS	27 (85% ♂)	RA (56%), VB (44%)	9.8 M	SMI	Significant increase in SMI.
Gioia et al. (2021)	RS	35 (80% ♂)	RA (54%), VB (46%)	19 M	SMI, SATI, and VATI	Significant increase in SMI and SATI and significant decrease in VATI.
Holland-Fischer et al. (2010)	-	11 (73% ♂)	RA (64%), RA+VB (36%)	6 M	W, BMI, BCM, LBM, and FM	Significant increase in all but FM.
Holland-Fischer et al. (2009)	-	17	RA (59%), VB (29%), both (12%)	13 M	W and BCM	Significant increase in BCM.
Jahangiri et al. (2019)	RS	76 (56.2% ♂)	RA/RH(52.6%), VB (47.4%)	13.5 M	SMA	Significant increase in SMA.
Liu et al. (2022)	RS	224 (71% ♂)	RA (14%), VB (86%)	12 M	SMA, SMI, SFA, SFT, AF W, and AF BMI	No significant change in SMA, SMI, SFA, and SFT in patients without sarcopenia. Significant increase in SMA, SMI, SFA, and SFT in patients with sarcopenia. No significant change in AF W and AF BMI in patients without ascites and sarcopenia. Significant increase in AF W and AF BMI in patients with sarcopenia but without ascites.
Montomoli et al. (2010)	PS	21	RA (57%), VB (33%), both (10%)	13M	BMI, FM, and DLM	No significant change in overweight patients, significant increase in dry lean mass in under/normal weight patients.
Nolte et al. (2003)	PS	31	RA, VB	9M	W, BMI, AF W, and AF BMI	Significant increase in W, BMI, AF W, and AF BMI in male patients, significant increase in AF W and AF BMI in female patients.
Pang et al. (2021)	RS	77	RA, VB	13M	W, BMI	Significant increase in W and BMI.
Plauth et al. (2004)	PS	21 (62% ♂)	RA (33%), VB (43%), both (24%)	12M	W, BMI, MAFA, MAMA, and BCM	Significant increase in W, BMI, and MAMA.
Thomsen et al. (2012)	-	25 (60% ♂)	RA (68%), VB (20%), both (12%)	6M	W, BMI, FM*, and BCM	Significant increase in BCM.
Trotter et al. (1998)	RS	35 (69% ♂)	RA	8.8M	W	Significant increase in W.
Tsien et al. (2012)	-	57 (63% ♂)	RA (72%), VB (25%), both (3%)	13.5M	BMI, SMA, VAT, and SAT	Significant increase in SMA and significant decrease in SAT.

Footnote: AF—ascitic-free, ASC—ascites, BCM—body cell mass (kg), BMI—body mass index (kg/m^2), DLM—dry lean mass (kg), FM—fat mass (% of total body weight/*kg), F10/F30—force of m. adductor policis (%), kg—kilogram, M—months, MAFA—mid-arm fat area, MAMA—mid-arm muscle area (cm^2), MRR—muscle relaxation rate (m. adductor policis) (%), SAT—subcutaneous adipose tissue (cm^3/3 mm), SATI—subcutaneous adipose tissue index (cm^2/m^2), SFA—subcutaneous fat area (cm^2), SFT—subcutaneous fat thickness (cm), SMA—skeletal muscle area (cm^2), SMI—skeletal muscle index (cm^2/m^2), TPMA—total psoas muscle area (mm^2), TPMT—transversal right psoas muscle thickness at the umbilical level/height (mm/m), TIPS—transjugular intrahepatic portosystemic shunt, VAT—visceral adipose tissue (cm^3/3 mm), VATI—visceral adipose tissue index (cm^2/m^2), VFA—visceral fat area (cm^2), W—weight (kg), -—no information.

Table 5. General characteristics of enrolled patients according to the development of HE during post-TIPS follow-up.

Characteristic	**Overall**, (n = 85)	**No HE group** (n= 50)	**HE group** (n = 35)	**p-value**
Age, yrs	59 (54, 66)	58 (52, 64)	62 (56, 67)	0.076
Sex, male	63 (74%)	40 (80%)	23 (66%)	0.2
BMI	24.5 (22.4, 27.4)	24.1 (22.1, 27.9)	25.0 (23.1, 27.1)	0.3
Alcohol	51 (61%)	34 (68%)	17 (50%)	0.1
Active alcohol use	18 (21%)	13 (26%)	5 (15%)	0.2
Hepatitis C	17 (20%)	8 (16%)	9 (26%)	0.2
Hepatitis B	3 (3.6%)	2 (4.0%)	1 (2.9%)	>0.9
Immunomediate liver disease	4 (4.8%)	4 (8.0%)	0 (0%)	0.14
Metabolic	27 (32%)	15 (30%)	12 (35%)	0.6
History				
Ascites	57 (68%)	34 (68%)	23 (68%)	NS
Varices, small	63 (75%)	38 (76%)	25 (74%)	
Varices, big	1 (1.2%)	0 (0%)	1 (2.9%)	
Hepatic encephalopathy	25 (30%)	15 (30%)	10 (29%)	
Hepatocarcinoma	11 (13%)	7 (14%)	4 (11%)	
Portal vein thrombosis	25 (29%)	15 (30%)	10 (29%)	
Diabetes	33 (39%)	18 (36%)	15 (43%)	0.5
Use of Rifaximin	21 (25%)	13 (26%)	8 (23%)	0.7
Use of Lactulose	37 (44%)	22 (44%)	15 (43%)	>0.9
At baseline				

Ascites	55 (65%)	31 (62%)	24 (69%)	0.052
Grade 1 2 3	12 (18%) 11 (17%) 32 (48%)	11 (29%) 6 (16%) 15 (39%)	5 (18% 1 (3.6%) 17 (61%)	
Active bleeding	17 (20%)	11 (22%)	6 (17%)	0.6
Portal vein thrombosis	29 (34%)	17 (34%)	12 (34%)	0.9
Cavernoma	3 (3.5%)	2 (4.0%)	1 (2.9%)	0.9
Hepatic Encephalopathy **Grade** 1 2 3	7 (8.2%) 2 (33%) 3 (50%) 1 (17%)	3 (6.0%) 1 (33%) 1 (33%) 1 (33%)	4 (11%) 1 (33%) 2 (67%) 1 (33%)	>0.9
C-Reactive Protein mg/dL	1.20 (0.50, 2.54)	1.02 (0.33, 2.48)	1.40 (0.76, 2.62)	0.3
Child-Pugh class				
A	29 (35%)	19 (38%)	10 (29%)	0.2
B	50 (60%)	30 (60%)	20 (59%)	0.2
C	5 (6.0%)	1 (2.0%)	4 (12%)	0.2
Child-Pugh score	7.00 (6.00, 8.00)	7.00 (6.00, 8.00)	7.50 (6.00, 8.75)	0.2
MELD	11.0 (9.0, 14.0)	10.0 (9.0, 14.0)	12.0 (10.2, 14.0)	0.13
MELD-Na	13.2 (10.8, 17.0)	13.0 (10.0, 16.0)	14.0 (11.0, 17.0)	0.2

*Data are presented as number of patients or means and % or SD in brackets, as appropriate

Table 6. Hemodynamic parameters at TIPS placement in patients with and without post-TIPS HE.

Characteristic	**Overall**, N = 85	**No HE group**, N = 50	**HE group**, N = 35	**p-value**
TIPS dilatation (mm)				0.6
5	3 (3.6%)	2 (4.2%)	1 (2.9%)	

6	17 (20%)	9 (19%)	8 (23%)	
7	7 (8.4%)	5 (10%)	2 (5.7%)	
8	34 (41%)	21 (44%)	13 (37%)	
9	17 (20%)	7 (15%)	10 (29%)	
10	5 (6.0%)	4 (8.3%)	1 (2.9%)	
PSPG PRE	21 (19, 25)	21 (18, 24)	21 (19, 26)	0.5
PSPG POST	12.0 (9.0, 14.0)	12.0 (9.0, 14.0)	12.0 (11.0, 14.2)	0.4
PSPG DELTA	9.0 (7.0, 12.2)	9.0 (7.0, 12.2)	8.5 (7.0, 13.2)	0.6

*Data are presented as number of patients or means and % or SD in brackets, as appropriate

Table 7. Comparison of muscle and adipose tissue parameters between patients with and without post-TIPS HE.

Characteristic	**Overall**, N = 85	**No HE group**, N = 50	**HE group**, N = 35	**p-value**
Muscle mass, cm²	138 (116, 155)	143 (111, 166)	133 (117, 148)	0.3
SMI, cm./m²	47 (39, 54)	48 (38, 55)	44 (39, 51)	0.5
Sarcopenia, yes (%)	47 (55%)	27 (54%)	20 (57%)	0.8
Muscle attenuation, HU	30 (26, 37)	30 (27, 37)	30 (25, 38)	0.6
Myosteatosis, yes	69 (81%)	42 (84%)	27 (77%)	0.4
Sarcomyosteatosis, yes (%)	41 (48%)	24 (48%)	17 (49%)	>0.9
Visceral Adipose Tissue, cm.	105 (65, 194)	106 (70, 203)	104 (59, 168)	0.5
Subcutaneous Adipose Tissue (SAT), cm²	130 (75, 235)	131 (80, 213)	130 (67, 259)	0.9
SAT Radiointensity (RSAT), HU	-90 (-97, -78)	-93 (-97, -80)	-87 (-97, -70)	0.3
High level of RSAT, yes (%)	20 (24%)	9 (18%)	11 (31%)	0.2
VAT/SAT ratio	0.92 (0.58, 1.28)	0.91 (0.59, 1.30)	0.92 (0.56, 1.21)	0.6

*Data are presented as number of patients or means and % or SD in brackets, as appropriate

Table 8. Comparison of muscle and adipose tissue parameters at the repeated CT scan between patients with and without post-TIPS HE.

Characteristic	**Overall**, N = 85	**No HE group**, N = 50	**HE group**, N = 35	**p-value**
Muscle mass, cm²	138 (124, 170)	152 (127, 176)	129 (119, 154)	0.078
SMI	48 (43, 59)	50 (44, 61)	46 (40, 55)	0.10
Sarcopenia, yes (%)	27 (45%)	13 (41%)	14 (50%)	0.5

Reversion of sarcopenia, yes (%)	10 (17%)	5 (16%)	5 (18%)	>0.9
Significant increase in SMI	36 (60%)	19 (59%)	17 (61%)	>0.9
Muscle attenuation, HU	31 (27, 36)	32 (29, 40)	29 (25, 34)	0.068
Myosteatosis, yes (%)	42 (71%)	21 (66%)	21 (78%)	0.3
Visceral Adipose Tissue, cm^2	99 (48, 144)	106 (56, 149)	93 (39, 136)	0.5
Subcutaneous Adipose Tissue (SAT), cm^2	159 (95, 252)	164 (106, 262)	158 (86, 242)	0.8
SAT Radiointensity (RSAT), HU	-90 (-97, -76)	-92 (-98, -88)	-87 (-96, -70)	0.2
High level of RSAT, yes (%)	13 (22%)	3 (9.4%)	10 (36%)	0.013
VAT/SAT ratio	0.55 (0.39, 0.78)	0.60 (0.40, 0.77)	0.51 (0.35, 0.83)	0.6

*Data are presented as number of patients or means and % or SD in brackets, as appropriate

Table 9. Body composition at baseline and after TIPS placement.

	Baseline CT scan	Repeated CT scan	Delta	p.value
SMI, cm^2/m^2	47.31 ± 11.13	49.91 ± 10.84	2.60	0.001
Muscle attenuation, HU	31.27 ± 7.63	31.88 ± 7.80	0.61	0.289
Subcutaneous Adipose Tissue (SAT), cm^2	167.51 ± 111.37	174.47 ± 108.81	6.95	0.096
Visceral Adipose Tissue, cm^2	143.22 ± 100.75	102.38 ± 70.32	-40.84	0.000
SAT Radiointensity (RSAT), HU	-87.64 ± 18.05	-83.93 ± 27.63	3.70	0.471
VAT/SAT ratio	0.98 ± 0.57	1.02 ± 2.32	0.04	0.000

*Data are presented as number of patients or means and % or SD in brackets, as appropriate

REFERENCES

1 - NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet*. 2024;403(10431):1027-1050. doi:10.1016/S0140-6736(23)02750-2

2 - Baker P, Hawkes C, Wingrove K, et al. What drives political commitment for nutrition? A review and framework synthesis to inform the United Nations Decade of Action on Nutrition. *BMJ Glob Health*. 2018;3(1):e000485. Published 2018 Feb 10. doi:10.1136/bmjgh-2017-000485

3 - Dent E, Wright ORL, Woo J, Hoogendijk EO. Malnutrition in older adults. Lancet. 2023;401(10380):951-966. doi:10.1016/S0140-6736(22)02612-5

4 - Falcon LJ, Harris-Love MO. Sarcopenia and the New ICD-10-CM Code: Screening, Staging, and Diagnosis Considerations. Fed Pract. 2017;34(7):24-32.

5 - Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16-31. doi:10.1093/ageing/afy169

6 - Petermann-Rocha F, Balntzi V, Gray SR, et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. 2022;13(1):86-99. doi:10.1002/jcsm.12783

7 - Beaudart C, Demonceau C, Reginster JY, et al. Sarcopenia and health-related quality of life: A systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. 2023;14(3):1228-1243. doi:10.1002/jcsm.13243

8 - Dlima SD, Hall A, Aminu AQ, Akpan A, Todd C, Vardy ERLC. Frailty: a global health challenge in need of local action. *BMJ Glob Health*. 2024;9(8):e015173. Published 2024 Aug 9. doi:10.1136/bmjgh-2024-015173

9 - Spiers GF, Kunonga TP, Hall A, et al. Measuring frailty in younger populations: a rapid review of evidence. *BMJ Open*. 2021;11(3):e047051. Published 2021 Mar 22. doi:10.1136/bmjopen-2020-047051

10 -Dondero K, Friedman B, Rekant J, Landers-Ramos R, Addison O. The effects of myosteatosis on skeletal muscle function in older adults. *Physiol Rep*. 2024;12(9):e16042. doi:10.14814/phy2.16042

11 - Oliver CJ, Climstein M, Rosic N, Bosy-Westphal A, Tinsley G, Myers S. Fat-Free Mass: Friend or Foe to Metabolic Health?. *J Cachexia Sarcopenia Muscle*. 2025;16(1):e13714. doi:10.1002/jcsm.13714

12 - Correa-de-Araujo R, Addison O, Miljkovic I, et al. Myosteatosis in the Context of Skeletal Muscle Function Deficit: An Interdisciplinary Workshop at the National Institute on Aging. *Front Physiol*. 2020;11:963. Published 2020 Aug 7. doi:10.3389/fphys.2020.00963

13 - Onyango AN. Cellular Stresses and Stress Responses in the Pathogenesis of Insulin Resistance. *Oxid Med Cell Longev*. 2018;2018:4321714. Published 2018 Jul 9. doi:10.1155/2018/4321714

14 - Miljkovic I, Zmuda JM. Epidemiology of myosteatosis. *Curr Opin Clin Nutr Metab Care*. 2010;13(3):260-264. doi:10.1097/MCO.0b013e328337d826

15 - Stout MB, Justice JN, Nicklas BJ, Kirkland JL. Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty. *Physiology (Bethesda)*. 2017;32(1):9-19. doi:10.1152/physiol.00012.2016

16 - Carter CS, Justice JN, Thompson L. Lipotoxicity, aging, and muscle contractility: does fiber type matter?. *Geroscience*. 2019;41(3):297-308. doi:10.1007/s11357-019-00077-z

17 - Marcucci L, Reggiani C. Increase of resting muscle stiffness, a less considered component of age-related skeletal muscle impairment. Eur J Transl Myol. 2020;30(2):8982. Published 2020 Jun 17. doi:10.4081/ejtm.2019.8982

18 - Dondero K, Friedman B, Rekant J, Landers-Ramos R, Addison O. The effects of myosteatosis on skeletal muscle function in older adults. *Physiol Rep*. 2024;12(9):e16042. doi:10.14814/phy2.16042

19 - Loomis T, Smith LR. Thrown for a loop: fibro-adipogenic progenitors in skeletal muscle fibrosis. *Am J Physiol Cell Physiol*. 2023;325(4):C895-C906. doi:10.1152/ajpcell.00245.2023

20 - Lieber RL, Binder-Markey BI. Biochemical and structural basis of the passive mechanical properties of whole skeletal muscle. *J Physiol*. 2021;599(16):3809-3823. doi:10.1113/JP280867

21 - Xu J, Wan CS, Ktoris K, Reijnierse EM, Maier AB. Sarcopenia Is Associated with Mortality in Adults: A Systematic Review and Meta-Analysis. *Gerontology*. 2022;68(4):361-376. doi:10.1159/000517099

22 - Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309(1):71-82. doi:10.1001/jama.2012.113905

23 - Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev*. 2010;11(1):11-18. doi:10.1111/j.1467-789X.2009.00623.x

24 - Kaess BM, Pedley A, Massaro JM, Murabito J, Hoffmann U, Fox CS. The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. *Diabetologia*. 2012;55(10):2622-2630. doi:10.1007/s00125-012-2639-5

25 - Liao CC, Fujimoto WY, Kahn SE, Leonetti DL, Boyko EJ. Abdominal visceral-to-subcutaneous fat ratio in the prediction of metabolic syndrome risk in Japanese Americans followed prospectively for 10-years loses information. *Obes Res Clin Pract*. 2024;18(4):263-268. doi:10.1016/j.orcp.2024.09.001

26 - Jung CH, Rhee EJ, Kwon H, Chang Y, Ryu S, Lee WY. Visceral-to-Subcutaneous Abdominal Fat Ratio Is Associated with Nonalcoholic Fatty Liver Disease and Liver Fibrosis. *Endocrinol Metab (Seoul)*. 2020;35(1):165-176. doi:10.3803/EnM.2020.35.1.165

27 - Buckley E, Mullen MM, Nizamuddin RA, et al. High visceral fat to subcutaneous fat ratios portend a poor prognosis in patients with advanced endometrial cancer. *Gynecol Oncol*. 2022;167(3):496-501. doi:10.1016/j.ygyno.2022.09.011

28 - He AQ, Li CQ, Zhang Q, Liu T, Liu J, Liu G. Visceral-to-Subcutaneous Fat Ratio Is a Potential Predictor of Postoperative Complications in Colorectal Cancer. *Med Sci Monit*. 2021;27:e930329. Published 2021 Jun 8. doi:10.12659/MSM.930329

29 - Gifford A, Walker RC, Towse TF, Brian Welch E. Correlations between quantitative fat-water magnetic resonance imaging and computed tomography in human subcutaneous white adipose tissue. *J Med Imaging (Bellingham)*. 2015;2(4):046001. doi:10.1117/1.JMI.2.4.046001

30 - Baba S, Jacene HA, Engles JM, Honda H, Wahl RL. CT Hounsfield units of brown adipose tissue increase with activation: preclinical and clinical studies. *J Nucl Med*. 2010;51(2):246-250. doi:10.2967/jnumed.109.068775

31 - Tilves C, Zmuda JM, Kuipers AL, et al. Associations of Thigh and Abdominal Adipose Tissue Radiodensity with Glucose and Insulin in Nondiabetic African-Ancestry Men. *Obesity (Silver Spring)*. 2020;28(2):404-411. doi:10.1002/oby.22695

32 - da Cunha AD Júnior, Silveira MN, Takahashi MES, et al. Adipose tissue radiodensity: A new prognostic biomarker in people with multiple myeloma. *Nutrition*. 2021;86:111141. doi:10.1016/j.nut.2021.111141

33 - Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309(1):71-82. doi:10.1001/jama.2012.113905

34 - Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev*. 2010;11(1):11-18. doi:10.1111/j.1467-789X.2009.00623.x

35 - Kaess BM, Pedley A, Massaro JM, Murabito J, Hoffmann U, Fox CS. The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. *Diabetologia*. 2012;55(10):2622-2630. doi:10.1007/s00125-012-2639-5

36 - Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;383(9930):1749-1761. doi:10.1016/S0140-6736(14)60121-5

37 - Bischoff SC, Bernal W, Dasarathy S, et al. ESPEN practical guideline: Clinical nutrition in liver disease. Clin Nutr. 2020;39(12):3533-3562. doi:10.1016/j.clnu.2020.09.001 PubMed+1

38 - Merli M, Berzigotti A, et al. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol. 2019;70(1): doi:10.1016/j.jhep.2018.06.024

39 - Merli M, Giusto M, Lucidi C, Giannelli V, Pentassuglio I, Di Gregorio V, Lattanzi B, Riggio O. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. Metab Brain Dis. 2013;28(2):281-284. doi:10.1007/s11011-012-9365-z

40 - Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: a systematic review and meta-analysis. PLoS One. 2017;12(10):e0186990. doi:10.1371/journal.pone.0186990 PLOS+3PLOS+3PubMed+3

41 - Tandon P, Raman M, Mourtzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. *Hepatology*. 2017;65(3):1044-1057. doi:10.1002/hep.29003

42 - Plauth M, Schütz ET. Cachexia in liver cirrhosis. *Int J Cardiol*. 2002;85(1):83-87. doi:10.1016/s0167-5273(02)00236-x

43 - Bhanji RA, Moctezuma-Velazquez C, Duarte-Rojo A, et al. Myosteatosis and sarcopenia are associated with hepatic encephalopathy in patients with cirrhosis. *Hepatol Int*. 2018;12(4):377-386. doi:10.1007/s12072-018-9875-9

44 - Lucidi C, Lattanzi B, Di Gregorio V, et al. A low muscle mass increases mortality in compensated cirrhotic patients with sepsis. *Liver Int*. 2018;38(5):851-857. doi:10.1111/liv.13691

45 - Merli M, Giusto M, Lucidi C, et al. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. *Metab Brain Dis*. 2013;28(2):281-284. doi:10.1007/s11011-012-9365-z

46 - Tandon P, Ney M, Irwin I, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl*. 2012;18(10):1209-1216. doi:10.1002/lt.23495

47 - Morgan AG, Kelleher J, Walker BE, Losowsky MS. Nutrition in cryptogenic cirrhosis and chronic aggressive hepatitis. *Gut*. 1976;17(2):113-118. doi:10.1136/gut.17.2.113

48 - Mendenhall CL, Anderson S, Weesner RE, Goldberg SJ, Crolic KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. *Am J Med*. 1984;76(2):211-222. doi:10.1016/0002-9343(84)90776-9

49 - Cui Y, Zhang M, Guo J, Jin J, Wang H, Wang X. Correlation between sarcopenia and cirrhosis: a meta-analysis. *Front Nutr*. 2024;10:1342100. Published 2024 Jan 10. doi:10.3389/fnut.2023.1342100

50 - Mazeaud S, Zupo R, Couret A, Panza F, Sardone R, Castellana F. Prevalence of Sarcopenia in Liver Cirrhosis: A Systematic Review and Meta-Analysis. *Clin Transl Gastroenterol*. 2023;14(7):e00584. Published 2023 Jul 1. doi:10.14309/ctg.0000000000000584

51 - Jiang MJ, Wu MC, Duan ZH, et al. Prevalence and clinical impact of sarcopenia in liver transplant recipients: A meta-analysis. *World J Gastroenterol*. 2024;30(8):956-968. doi:10.3748/wjg.v30.i8.956

52 - Wei S, Nguyen TT, Zhang Y, Ryu D, Gariani K. Sarcopenic obesity: epidemiology, pathophysiology, cardiovascular disease, mortality, and management. *Front Endocrinol (Lausanne)*. 2023;14:1185221. Published 2023 Jun 30. doi:10.3389/fendo.2023.1185221

53 - Eslamparast T, Montano-Loza AJ, Raman M, Tandon P. Sarcopenic obesity in cirrhosis-The confluence of 2 prognostic titans. *Liver Int*. 2018;38(10):1706-1717. doi:10.1111/liv.13876

54 - Tantai X, Liu Y, Yeo YH, et al. Effect of sarcopenia on survival in patients with cirrhosis: a meta-analysis. *J Hepatol*. 2022;76(3):588-599. doi:10.1016/j.jhep.2021.11.006

55 - Prokopidis K, Affronti M, Testa GD, et al. Sarcopenia increases mortality risk in liver transplantation: a systematic review and meta-analysis. *Panminerva Med*. 2024;66(1):47-54. doi:10.23736/S0031-0808.23.04863-2

56 - Zhou D, et al. Impact of sarcopenia on the survival of patients undergoing liver transplantation for decompensated liver cirrhosis. *J Cachexia Sarcopenia Muscle*. 2023;14(6):2602-2612. doi:10.1002/jcsm.13334

57 - Bhanji RA, Moctezuma-Velazquez C, Duarte-Rojo A, et al. Myosteatosis and sarcopenia are associated with hepatic encephalopathy in patients with cirrhosis. Hepatol Int. 2018;12(4):377-386. doi:10.1007/s12072-018-9875-9

58 - Di Cola S, Nardelli S, Ridola L, Gioia S, Riggio O, Merli M. Ammonia and the Muscle: An Emerging Point of View on Hepatic Encephalopathy. J Clin Med. 2022;11(3):611. Published 2022 Jan 26. doi:10.3390/jcm11030611

*59 - Wongtrakul W, Bandidniyamanon W, Charatcharoenwitthaya P, et al. Relati*onship between sarcopenia and minimal hepatic encephalopathy in patients with cirrhosis: a prospective observational study. *BMC Gastroenterol*. 2025;25(1):88. doi:10.1186/s12876-025-03674-9

60- Wijarnpreecha K, Werlang M, Panjawatanan P, Kroner PT, Cheungpasitporn W, Lukens FJ, Pungpapong S, Ungprasert P. Association between sarcopenia and hepatic encephalopathy: a systematic review and meta-analysis. *Annals of hepatology*. 2020;19(3):245-250. doi:10.1016/j.aohep.2019.06.007

61 - Gairing SJ, Schleicher EM, Galle PR, Labenz C. Prediction and prevention of the first episode of overt hepatic encephalopathy in patients with cirrhosis. *Hepatol Commun*. 2023;7(4):e0096. Published 2023 Mar 17. doi:10.1097/HC9.0000000000000096

62 - Hanai T, Shiraki M, Watanabe S, et al. Sarcopenia predicts minimal hepatic encephalopathy in patients with liver cirrhosis. *Hepatol Res*. 2017;47(13):1359-1367. doi:10.1111/hepr.12873

63 - Choudhary NS, Kumar N, Duseja A. Peroxisome Proliferator-Activated Receptors and Their Agonists in Nonalcoholic Fatty Liver Disease. *J Clin Exp Hepatol*. 2019;9(6):731-739. doi:10.1016/j.jceh.2019.06.004

64 - Nardelli S, Lattanzi B, Merli M, et al. Muscle Alterations Are Associated With Minimal and Overt Hepatic Encephalopathy in Patients With Liver Cirrhosis. *Hepatology*. 2019;70(5):1704-1713. doi:10.1002/hep.30692

65 - Mauro E, Crespo G, Martinez-Garmendia A, et al. Cystatin C and Sarcopenia Predict Acute on Chronic Liver Failure Development and Mortality in Patients on the Liver Transplant Waiting List. *Transplantation*. 2020;104(7):e188-e198. doi:10.1097/TP.0000000000003222

66 - Topan MM, Sporea I, Dănilă M, et al. Impact of Sarcopenia on Survival and Clinical Outcomes in Patients With Liver Cirrhosis. *Front Nutr*. 2021;8:766451. Published 2021 Oct 21. doi:10.3389/fnut.2021.766451

67 - Iacob S, Mina V, Mandea M, et al. Assessment of Sarcopenia Related Quality of Life Using SarQoL® Questionnaire in Patients With Liver Cirrhosis. *Front Nutr*. 2022;9:774044. Published 2022 Feb 25. doi:10.3389/fnut.2022.774044

68 - Lattanzi B, Nardelli S, Pigliacelli A, et al. The additive value of sarcopenia, myosteatosis and hepatic encephalopathy in the predictivity of model for end-stage liver disease. *Dig Liver Dis*. 2019;51(11):1508-1512. doi:10.1016/j.dld.2019.09.004

69 - Tandon P, Montano-Loza AJ, Lai JC, Dasarathy S, Merli M. Sarcopenia and frailty in decompensated cirrhosis. *J Hepatol*. 2021;75 Suppl 1(Suppl 1):S147-S162. doi:10.1016/j.jhep.2021.01.025

70 - Lai JC, Rahimi RS, Verna EC, et al. Frailty Associated With Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multicenter Study. *Gastroenterology*. 2019;156(6):1675-1682. doi:10.1053/j.gastro.2019.01.028

71 - Kobashigawa J, Dadhania D, Bhorade S, et al. Report from the American Society of Transplantation on frailty in solid organ transplantation. *Am J Transplant*. 2019;19(4):984-994. doi:10.1111/ajt.15198

72 - D'Arcangelo F, Zanetto A, Ferrarese A, et al. Frailty and sarcopenia in patients with cirrhosis awaiting liver transplantation: evidence from a single-centre, prospective cohort study. *Updates Surg*. 2024;76(5):1807-1818. doi:10.1007/s13304-024-01962-9

73 - Lai JC, Covinsky KE, Dodge JL, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology*. 2017;66(2):564-574. doi:10.1002/hep.29219

74 - Lai JC, Dodge JL, Kappus MR, et al. Changes in frailty are associated with waitlist mortality in patients with cirrhosis. *J Hepatol*. 2020;73(3):575-581. doi:10.1016/j.jhep.2020.03.029

75 - Kamiliou A, Lekakis V, Chrysavgis L, Cholongitas E. Prevalence and impact on the outcome of myosteatosis in patients with cirrhosis: a systematic review and meta-analysis. *Hepatol Int*. 2024;18(2):688-699. doi:10.1007/s12072-023-10632-8

76 - Montano-Loza AJ, Angulo P, Meza-Junco J, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. *J Cachexia Sarcopenia Muscle*. 2016;7(2):126-135. doi:10.1002/jcsm.12039

77 - Xue H, Liu Y, Liu Y, et al. Myosteatosis and the clinical outcomes of patients with liver cirrhosis: A meta-analysis. *PLoS One*. 2024;19(9):e0310017. Published 2024 Sep 12. doi:10.1371/journal.pone.0310017

78 - Di Cola S, D'Amico G, Motamedrad M, Montano-Loza A, Merli M. Study protocol to redefine muscle attenuation cut-offs for better prediction of mortality in patients with cirrhosis: a comprehensive post hoc validation study - a study protocol. *BMJ Open*. 2025;15(3):e094252. Published 2025 Mar 25. doi:10.1136/bmjopen-2024-094252

79 - Wang X, Sun M, Li Y, et al. Association of myosteatosis with various body composition abnormalities and longer length of hospitalization in patients with decompensated cirrhosis. *Front Nutr*. 2022;9:921181. Published 2022 Sep 15. doi:10.3389/fnut.2022.921181

80 - Feng H, Wang X, Mao L, et al. Relationship between sarcopenia/myosteatosis and frailty in hospitalized patients with cirrhosis: a sex-stratified analysis. *Ther Adv Chronic Dis*. 2021;12:20406223211026996. Published 2021 Jul 27. doi:10.1177/20406223211026996

81 - Johnston HE, Andelkovic M, Mayr HL, et al. Myosteatosis Is Associated With Frailty and Poor Physical Function in Patients Undergoing Liver Transplant Evaluation: A Cohort Study. *Clin Transplant*. 2024;38(12):e70034. doi:10.1111/ctr.70034

82 - Geladari E, Alexopoulos T, Kontogianni MD, et al. The Presence of Myosteatosis Is Associated with Age, Severity of Liver Disease and Poor Outcome and May Represent a Prodromal Phase of Sarcopenia in Patients with Liver Cirrhosis. *J Clin Med*. 2023;12(9):3332. Published 2023 May 7. doi:10.3390/jcm12093332

83 - Kimura N, Tsuchiya A, Oda C, et al. Visceral Adipose Tissue Index and Hepatocellular Carcinoma Are Independent Predictors of Outcome in Patients with Cirrhosis Having Endoscopic Treatment for Esophageal Varices. *Dig Dis*. 2021;39(1):58-65. doi:10.1159/000508867

84 - Terjimanian MN, Harbaugh CM, Hussain A, et al. Abdominal adiposity, body composition and survival after liver transplantation. *Clin Transplant*. 2016;30(3):289-294. doi:10.1111/ctr.12688

85 - Montano-Loza AJ, Mazurak VC, Ebadi M, et al. Visceral adiposity increases risk for hepatocellular carcinoma in male patients with cirrhosis and recurrence after liver transplant. *Hepatology*. 2018;67(3):914-923. doi:10.1002/hep.29578

86 - Ebadi M, Tandon P, Moctezuma-Velazquez C, et al. Low subcutaneous adiposity associates with higher mortality in female patients with cirrhosis. *J Hepatol*. 2018;69(3):608-616. doi:10.1016/j.jhep.2018.04.015

87 - Rodrigues SG, Brabandt B, Stirnimann G, Maurer MH, Berzigotti A. Adipopenia correlates with higher portal pressure in patients with cirrhosis. *Liver Int*. 2019;39(9):1672-1681. doi:10.1111/liv.14175

88 - Parikh ND, Zhang P, Singal AG, et al. Body Composition Predicts Survival in Patients with Hepatocellular Carcinoma Treated with Transarterial Chemoembolization. *Cancer Res Treat*. 2018;50(2):530-537. doi:10.4143/crt.2017.156

89 - Ebadi M, Moctezuma-Velazquez C, Meza-Junco J, et al. Visceral Adipose Tissue Radiodensity Is Linked to Prognosis in Hepatocellular Carcinoma Patients Treated with Selective Internal Radiation Therapy. *Cancers (Basel)*. 2020;12(2):356. Published 2020 Feb 4. doi:10.3390/cancers12020356

90 -Tapper EB, Zhang P, Garg R, et al. Body composition predicts mortality and decompensation in compensated cirrhosis patients: A prospective cohort study. *JHEP Rep*. 2019;2(1):100061. Published 2019 Dec 5. doi:10.1016/j.jhepr.2019.11.005

91 - Ebadi M, Dunichand-Hoedl AR, Rider E, et al. Higher subcutaneous adipose tissue radiodensity is associated with increased mortality in patients with cirrhosis. *JHEP Rep*. 2022;4(7):100495. Published 2022 Apr 27. doi:10.1016/j.jhepr.2022.100495

92 - Cederholm T, Jensen GL, Correia MITD, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr*. 2019;38(1):1-9. doi:10.1016/j.clnu.2018.08.002

93 - Aghdassi AA, Schneider A, Kahl M, et al. Analysis of lifestyle factors in patients with concomitant chronic pancreatitis and liver cirrhosis. *Pancreatology*. 2017;17(5):698-705. doi:10.1016/j.pan.2017.07.194

94 - Bauer TM, Steinbrückner B, Brinkmann FE, et al. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. *Am J Gastroenterol*. 2001;96(10):2962-2967. doi:10.1111/j.1572-0241.2001.04668.x

95 - Bahr MJ, Ockenga J, Böker KH, Manns MP, Tietge UJ. Elevated resistin levels in cirrhosis are associated with the proinflammatory state and altered hepatic glucose metabolism but not with insulin resistance. *Am J Physiol Endocrinol Metab*. 2006;291(2):E199-E206. doi:10.1152/ajpendo.00291.2005

96 - Marchesini G, Bianchi G, Lucidi P, Villanova N, Zoli M, De Feo P. Plasma ghrelin concentrations, food intake, and anorexia in liver failure. *J Clin Endocrinol Metab*. 2004;89(5):2136-2141. doi:10.1210/jc.2003-031771

97 - Conchillo M, de Knegt RJ, Payeras M, et al. Insulin-like growth factor I (IGF-I) replacement therapy increases albumin concentration in liver cirrhosis: results of a pilot randomized controlled clinical trial. *J Hepatol*. 2005;43(4):630-636. doi:10.1016/j.jhep.2005.03.025

98 - Butterworth RF. L-Ornithine L-Aspartate for the Treatment of Sarcopenia in Chronic Liver Disease: The Taming of a Vicious Cycle. *Can J Gastroenterol Hepatol*. 2019;2019:8182195. Published 2019 Apr 28. doi:10.1155/2019/8182195

99 - Bémeur C, Butterworth RF. Reprint of: Nutrition in the Management of Cirrhosis and its Neurological Complications. *J Clin Exp Hepatol*. 2015;5(Suppl 1):S131-S140. doi:10.1016/j.jceh.2015.02.004

100 - Müller MJ, Böttcher J, Selberg O, et al. Hypermetabolism in clinically stable patients with liver cirrhosis. *Am J Clin Nutr*. 1999;69(6):1194-1201. doi:10.1093/ajcn/69.6.1194

101 - Khan S, Sansoni S, Di Cola S, Lapenna L, Merli M. A Comparative Study of Dietary Intake, Nutritional Status, and Frailty in Outpatients and Inpatients with Liver Cirrhosis. *Nutrients*. 2025;17(3):580. Published 2025 Feb 5. doi:10.3390/nu17030580

102 - Meyer F, Bannert K, Wiese M, et al. Molecular Mechanism Contributing to Malnutrition and Sarcopenia in Patients with Liver Cirrhosis. *Int J Mol Sci*. 2020;21(15):5357. Published 2020 Jul 28. doi:10.3390/ijms21155357

103 - Davuluri G, Giusto M, Chandel R, et al. Impaired Ribosomal Biogenesis by Noncanonical Degradation of β-Catenin during Hyperammonemia. *Mol Cell Biol*. 2019;39(16):e00451-18. Published 2019 Jul 29. doi:10.1128/MCB.00451-18

104 - Davuluri G, Krokowski D, Guan BJ, et al. Metabolic adaptation of skeletal muscle to hyperammonemia drives the beneficial effects of l-leucine in cirrhosis. *J Hepatol*. 2016;65(5):929-937. doi:10.1016/j.jhep.2016.06.004

105 - Motamedrad M, Ebadi M, Sanchez-Fernandez N, et al. Type II fibre atrophy and nuclear disruption in decompensated cirrhosis. *JHEP Rep*. 2025;7(9):101455. Published 2025 May 24. doi:10.1016/j.jhepr.2025.101455

106 - Ebadi M, Tsien C, Bhanji RA, et al. Myosteatosis in Cirrhosis: A Review of Diagnosis, Pathophysiological Mechanisms and Potential Interventions. *Cells*. 2022;11(7):1216. Published 2022 Apr 4. doi:10.3390/cells11071216

107 - Hua N, Takahashi H, Yee GM, et al. Influence of muscle fiber type composition on early fat accumulation under high-fat diet challenge. *PLoS One*. 2017;12(8):e0182430. Published 2017 Aug 1. doi:10.1371/journal.pone.0182430

108 - Perkisas S, De Cock AM, Verhoeven V, Vandewoude M. Intramuscular Adipose Tissue and the Functional Components of Sarcopenia in Hospitalized Geriatric Patients. *Geriatrics (Basel)*. 2017;2(1):11. Published 2017 Feb 22. doi:10.3390/geriatrics2010011

109 - Mastrocola R, Collino M, Nigro D, et al. Accumulation of advanced glycation end-products and activation of the SCAP/SREBP Lipogenetic pathway occur in diet-induced obese mouse skeletal muscle. *PLoS One*. 2015;10(3):e0119587. Published 2015 Mar 9. doi:10.1371/journal.pone.0119587

110 - Davuluri G, Allawy A, Thapaliya S, et al. Hyperammonaemia-induced skeletal muscle mitochondrial dysfunction results in cataplerosis and oxidative stress. *J Physiol*. 2016;594(24):7341-7360. doi:10.1113/JP272796

111 - Stretch C, Aubin JM, Mickiewicz B, et al. Sarcopenia and myosteatosis are accompanied by distinct biological profiles in patients with pancreatic and periampullary adenocarcinomas. *PLoS One*. 2018;13(5):e0196235. Published 2018 May 3. doi:10.1371/journal.pone.0196235

112 - Zoico E, Rossi A, Di Francesco V, et al. Adipose tissue infiltration in skeletal muscle of healthy elderly men: relationships with body composition, insulin resistance, and inflammation at the systemic and tissue level. *J Gerontol A Biol Sci Med Sci*. 2010;65(3):295-299. doi:10.1093/gerona/glp155

113 - Brehm A, Krssak M, Schmid AI, Nowotny P, Waldhäusl W, Roden M. Increased lipid availability impairs insulin-stimulated ATP synthesis in human skeletal muscle. *Diabetes*. 2006;55(1):136-140.

114 - Tardif N, Salles J, Guillet C, et al. Muscle ectopic fat deposition contributes to anabolic resistance in obese sarcopenic old rats through eIF2α activation. *Aging Cell*. 2014;13(6):1001-1011. doi:10.1111/acel.12263

115 - Marjot T, Armstrong MJ, Stine JG. Skeletal muscle and MASLD: Mechanistic and clinical insights. *Hepatol Commun*. 2025;9(6):e0711. Published 2025 May 23. doi:10.1097/HC9.0000000000000711

116 - Lundbom J. Adipose tissue and liver. *J Appl Physiol (1985)*. 2018;124(1):162-167. doi:10.1152/japplphysiol.00399.2017

117 - Hannukainen JC, Kalliokoski KK, Borra RJ, et al. Higher free fatty acid uptake in visceral than in abdominal subcutaneous fat tissue in men. *Obesity (Silver Spring)*. 2010;18(2):261-265. doi:10.1038/oby.2009.267

118 - Skamarauskas JT, Oakley F, Smith FE, et al. Noninvasive in vivo magnetic resonance measures of glutathione synthesis in human and rat liver as an oxidative stress biomarker. *Hepatology*. 2014;59(6):2321-2330. doi:10.1002/hep.26925

119 - European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;70(1):172-193. doi:10.1016/j.jhep.2018.06.024

120 - Borhofen SM, Gerner C, Lehmann J, et al. The Royal Free Hospital-Nutritional Prioritizing Tool Is an Independent Predictor of Deterioration of Liver Function and Survival in Cirrhosis. *Dig Dis Sci*. 2016;61(6):1735-1743. doi:10.1007/s10620-015-4015-z

121 - Kondrup J, Rasmussen HH, Hamberg O, Stanga Z; Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321-336. doi:10.1016/s0261-5614(02)00214-5

122 - Gomes-Neto AW, van Vliet IMY, Osté MCJ, et al. Malnutrition Universal Screening Tool and Patient-Generated Subjective Global Assessment Short Form and their predictive validity in hospitalized patients. *Clin Nutr ESPEN*. 2021;45:252-261. doi:10.1016/j.clnesp.2021.08.015

123 - Bischoff SC, Bernal W, Dasarathy S, et al. ESPEN practical guideline: Clinical nutrition in liver disease. *Clin Nutr*. 2020;39(12):3533-3562. doi:10.1016/j.clnu.2020.09.001

124 - Carey EJ, Lai JC, Wang CW, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. *Liver Transpl*. 2017;23(5):625-633. doi:10.1002/lt.24750

125 - Guo G, Yang W, Wang S, et al. Handgrip strength is a substitutive metric to the GLIM criteria-defined malnutrition and predicts long-term mortality among hospitalized patients with cirrhosis. *Nutr Clin Pract*. 2023;38(5):1021-1031. doi:10.1002/ncp.10983

126 - Nardelli S, Gioia S, Ridola L, et al. Risk of falls in patients with cirrhosis evaluated by timed up and go test: Does muscle or brain matter more?. *Dig Liver Dis*. 2022;54(3):371-377. doi:10.1016/j.dld.2021.06.019

127 - Becchetti C, Berzigotti A. Ultrasonography as a diagnostic tool for sarcopenia in patients with cirrhosis: Examining the pros and cons. *Eur J Intern Med*. 2023;116:27-33. doi:10.1016/j.ejim.2023.06.019

128 - Campani F, Li Cavoli TV, Arena U, Marra F, Lynch EN, Campani C. Quick and easy assessment of sarcopenia in cirrhosis: Can ultrasound be the solution?. *World J Gastroenterol*. 2024;30(17):2287-2293. doi:10.3748/wjg.v30.i17.2287

129 - Gagliard R. Campadello P. Brocco S. et al. Rectus femoris ultrasound identifies sarcopenia and predicts poor outcomes in patients with an acute decompensation of cirrhosis JHEP Rep Aug 2025 10.1016/j.jhepr.2025.101564

130 - Henin G, Lanthier N. What references and what gold standard should be used to assess myosteatosis in chronic liver disease?. J Hepatol. 2024;81(6):e273-e274. doi:10.1016/j.jhep.2024.07.003

131 - Carlier PG, Marty B, Scheidegger O, et al. Skeletal Muscle Quantitative Nuclear Magnetic Resonance Imaging and Spectroscopy as an Outcome Measure for Clinical Trials. *J Neuromuscul Dis*. 2016;3(1):1-28. doi:10.3233/JND-160145

132 - Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31(12):1539-1547. doi:10.1200/JCO.2012.45.2722

133 - Shan D, Zhang G, Du Z. Reevaluating myosteatosis criteria in cirrhosis: Fluid and gender considerations. *J Hepatol*. 2024;81(4):e192-e193. doi:10.1016/j.jhep.2024.06.005

134 - Ebadi M, Tsien C, Bhanji RA, et al. Skeletal Muscle Pathological Fat Infiltration (Myosteatosis) Is Associated with Higher Mortality in Patients with Cirrhosis. *Cells*. 2022;11(8):1345. Published 2022 Apr 14. doi:10.3390/cells11081345

135 - Kvist H, Sjöström L, Tylén U. Adipose tissue volume determinations in women by computed tomography: technical considerations. *Int J Obes*. 1986;10(1):53-67.

136 - Vehmas T, Kairemo KJ, Taavitsainen MJ. Measuring visceral adipose tissue content from contrast enhanced computed tomography. *Int J Obes Relat Metab Disord*. 1996;20(6):570-573.

137 - Zhu M, Li H, Yin Y, et al. U-shaped relationship between subcutaneous adipose tissue index and mortality in liver cirrhosis. *J Cachexia Sarcopenia Muscle*. 2023;14(1):508-516. doi:10.1002/jcsm.13154

138 - Di Cola S, Khan S, Lapenna L, Merli M. Emerging drugs for the treatment of sarcopenia in cirrhosis of the liver. *Expert Opin Emerg Drugs*. 2024;29(2):81-91. doi:10.1080/14728214.2024.2332428

139 - Lattanzi B, Bruni A, Di Cola S, et al. The Effects of 12-Week Beta-Hydroxy-Beta-Methylbutyrate Supplementation in Patients with Liver Cirrhosis: Results from a Randomized Controlled Single-Blind Pilot Study. *Nutrients*. 2021;13(7):2296. Published 2021 Jul 2. doi:10.3390/nu13072296

140 - Bruno BJ, Weavil JC, Ogle J, et al. Oral LPCN 1148 improves sarcopenia and hepatic encephalopathy in male patients with cirrhosis: A randomized, placebo-controlled phase 2 trial. *Hepatology*. 2025;81(6):1764-1775. doi:10.1097/HEP.0000000000001146

141 - Lopez-Delgado JC, Ballus J, Esteve F, et al. Outcomes of abdominal surgery in patients with liver cirrhosis. *World J Gastroenterol*. 2016;22(9):2657-2667. doi:10.3748/wjg.v22.i9.2657

142 - Tantai X, Liu Y, Yeo YH, et al. Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis. *J Hepatol*. 2022;76(3):588-599. doi:10.1016/j.jhep.2021.11.006

143 - Kaltenbach MG, Mahmud N. Assessing the risk of surgery in patients with cirrhosis. *Hepatol Commun*. 2023;7(4):e0086. Published 2023 Mar 30. doi:10.1097/HC9.0000000000000086

144 - Ghumman U, Lee B, Bigham D, Tsai E. Sarcopenia in cirrhosis: a clinical practice review. *Ann Palliat Med*. 2025;14(3):255-268. doi:10.21037/apm-24-173

145 - Di Cola S, Lapenna L, Gazda J, et al. Role of Transjugular Intrahepatic Portosystemic Shunt in the Liver Transplant Setting. *J Clin Med*. 2024;13(2):600. Published 2024 Jan 21. doi:10.3390/jcm13020600

146 - European Association for the Study of the Liver. EASL Clinical Practice Guidelines on TIPS. *J Hepatol*. 2025;83(1):177-210. doi:10.1016/j.jhep.2025.01.029

147 - Tripathi D, Stanley AJ, Hayes PC, et al. Transjugular intrahepatic portosystemic stent-shunt in the management of portal hypertension. *Gut*. 2020;69(7):1173-1192. doi:10.1136/gutjnl-2019-320221

148 - Li J, Feng D, Pang N, et al. Controlling nutritional status score as a new indicator of overt hepatic encephalopathy in cirrhotic patients following transjugular intrahepatic portosystemic shunt. *Clin Nutr*. 2022;41(2):560-566. doi:10.1016/j.clnu.2021.12.036

149 - Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp*. 2005;20(1):38-45.

150- de Felice I, Ridola L, Riggio O, Faccioli J, Nardelli S, Gioia S. Transjugular Intrahepatic Portosystemic Shunt Placement: Effects on Nutritional Status in Cirrhotic Patients. *J Clin Med*. 2023;12(22):7029. Published 2023 Nov 10. doi:10.3390/jcm12227029

151 - Vanderschueren E, Meersseman P, Wilmer A, et al. Sarcopenia in patients receiving TIPS is independently associated with increased risk of complications and mortality. *Dig Liver Dis*. 2025;57(2):549-557. doi:10.1016/j.dld.2024.10.013

152 - Stoffel E, Hwang SY, Qian X, Geller B, Morelli G, Zhang W. Sarcopenia is an independent risk factor for short-term mortality in patients undergoing transjugular intrahepatic

portosystemic shunt. *Eur J Gastroenterol Hepatol*. 2024;36(8):1010-1015. doi:10.1097/MEG.0000000000002790

153 - Büttner L, Aigner A, Stegherr R, et al. Sarcopenia as a Risk Factor in Patients Undergoing Transjugular Intrahepatic Portosystemic Shunt (TIPS) Implantation. *Diagnostics (Basel)*. 2025;15(11):1440. Published 2025 Jun 5. doi:10.3390/diagnostics15111440

154 - Nardelli S, Lattanzi B, Torrisi S, et al. Sarcopenia Is Risk Factor for Development of Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt Placement. *Clin Gastroenterol Hepatol*. 2017;15(6):934-936. doi:10.1016/j.cgh.2016.10.028

155 - Gairing SJ, Müller L, Kloeckner R, Galle PR, Labenz C. Review article: post-TIPSS hepatic encephalopathy-current knowledge and future perspectives. *Aliment Pharmacol Ther*. 2022;55(10):1265-1276. doi:10.1111/apt.16825

156 - Praktiknjo M, Clees C, Pigliacelli A, et al. Sarcopenia Is Associated With Development of Acute-on-Chronic Liver Failure in Decompensated Liver Cirrhosis Receiving Transjugular Intrahepatic Portosystemic Shunt. *Clin Transl Gastroenterol*. 2019;10(4):e00025. doi:10.14309/ctg.0000000000000025

157 - Yin L, Chu SL, Lv WF, et al. Contributory roles of sarcopenia and myosteatosis in development of overt hepatic encephalopathy and mortality after transjugular intrahepatic portosystemic shunt. *World J Gastroenterol*. 2023;29(18):2875-2887. doi:10.3748/wjg.v29.i18.2875

158 - Liu J, Yang C, Yao J, et al. Improvement of sarcopenia is beneficial for prognosis in cirrhotic patients after TIPS placement. *Dig Liver Dis*. 2023;55(7):918-925. doi:10.1016/j.dld.2023.01.001

159 - Shi W, Yin H, Yu Z, et al. Myosteatosis is an independent risk factor for overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunting. *Eur J Gastroenterol Hepatol*. 2024;36(7):897-903. doi:10.1097/MEG.0000000000002729

160 - Li S, Li Y, Zhou C, et al. Muscle fat content correlates with postoperative survival of viral-related cirrhosis patients after the TIPS: a retrospective study. *Ann Med*. 2025;57(1):2484460. doi:10.1080/07853890.2025.2484460

161 - Zhang B, Cai W, Gao F, et al. Prediction of Patient Survival with Psoas Muscle Density Following Transjugular Intrahepatic Portosystemic Shunts: A Retrospective Cohort Study. *Med Sci Monit*. 2022;28:e934057. Published 2022 Jan 15. doi:10.12659/MSM.934057

162 - Cheng S, Hu G, Jin Z, Wang Z, Xue H. Prediction of Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt Based on CT Radiomic Features of Visceral Adipose Tissue. *Acad Radiol*. 2024;31(5):1849-1861. doi:10.1016/j.acra.2023.10.013

163 - Wang C, Teng Y, Gao J, Zhang Z, Li Y. Low adipose tissue index as an indicator of hepatic encephalopathy in cirrhotic patients following transjugular intrahepatic portosystemic shunt. *Abdom Radiol (NY)*. 2023;48(4):1454-1467. doi:10.1007/s00261-023-03813-4

164 - Tiede A, Stockhoff L, Ehrenbauer AF, et al. Value of systemic inflammation markers for the detection of minimal and prediction of overt hepatic encephalopathy after TIPS insertion. *Metab Brain Dis*. 2024;40(1):58. Published 2024 Dec 10. doi:10.1007/s11011-024-01436-2

165 - Trotter JF, Suhocki PV, Rockey DC. Transjugular intrahepatic portosystemic shunt (TIPS) in patients with refractory ascites: effect on body weight and Child-Pugh score. *Am J Gastroenterol*. 1998;93(10):1891-1894. doi:10.1111/j.1572-0241.1998.00544.x

166 - Gioia S, Ridola L, Cristofaro L, et al. The improvement in body composition including subcutaneous and visceral fat reduces ammonia and hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. *Liver Int*. 2021;41(12):2965-2973. doi:10.1111/liv.15060

167 - Gioia S, Ridola L, Cristofaro L, et al. The improvement in body composition including subcutaneous and visceral fat reduces ammonia and hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. *Liver Int*. 2021;41(12):2965-2973. doi:10.1111/liv.15060

168 - Suzuki T, Farsad K. Impact of Changes in Body Composition after Transjugular Intrahepatic Portosystemic Shunt Creation on Morbidity and Mortality: A Systematic Review. *Tech Vasc Interv Radiol*. 2025;28(3):101060. doi:10.1016/j.tvir.2025.101060

169 - Huang S, Liu J, Cai J, et al. Predictors of Improvement of Sarcopenia after Transjugular Intrahepatic Portosystemic Shunt Creation in Cirrhotic Patients. *J Vasc Interv Radiol*. 2023;34(4):639-644. doi:10.1016/j.jvir.2022.12.474

170 - Liu J, Ma J, Yang C, et al. Sarcopenia in Patients with Cirrhosis after Transjugular Intrahepatic Portosystemic Shunt Placement. *Radiology*. 2022;303(3):711-719. doi:10.1148/radiol.211172

171 - Tuifua TS, Kapoor B, Partovi S, et al. Prediction of Mortality and Hepatic Encephalopathy after Transjugular Intrahepatic Portosystemic Shunt Placement: Baseline and Longitudinal Body Composition Measurement. *J Vasc Interv Radiol*. 2024;35(5):648-657.e1. doi:10.1016/j.jvir.2024.01.012

172 - Gioia S, Ridola L, Cristofaro L, et al. The improvement in body composition including subcutaneous and visceral fat reduces ammonia and hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. *Liver Int*. 2021;41(12):2965-2973. doi:10.1111/liv.15060

173 - Ronald J, Bozdogan E, Zaki IH, et al. Relative Sarcopenia With Excess Adiposity Predicts Survival After Transjugular Intrahepatic Portosystemic Shunt Creation. *AJR Am J Roentgenol*. 2020;214(1):200-205. doi:10.2214/AJR.19.21655

174 - Di Cola S, D'Amico G, Caraceni P, et al. Myosteatosis is closely associated with sarcopenia and significantly worse outcomes in patients with cirrhosis. *J Hepatol*. 2024;81(4):641-650. doi:10.1016/j.jhep.2024.05.020

175 - Gazda J, Di Cola S, Lapenna L, Khan S, Merli M. The Impact of Transjugular Intrahepatic Portosystemic Shunt on Nutrition in Liver Cirrhosis Patients: A Systematic Review. *Nutrients*. 2023;15(7):1617. Published 2023 Mar 27. doi:175

176 - Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16-31. doi:10.1093/ageing/afy169

177 - Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142-148. doi:10.1111/j.1532-5415.1991.tb01616.x

178 - Lai JC, Tandon P, Bernal W, et al. Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;74(3):1611-1644. doi:10.1002/hep.32049

179 - Tachi Y, Kozuka A, Hirai T, et al. Impact of myosteatosis on skeletal muscle volume loss in patients with chronic liver disease. *J Gastroenterol Hepatol*. Published online February 27, 2018. doi:10.1111/jgh.14133

180 - Kirk B, Al Saedi A, Duque G. Osteosarcopenia: A case of geroscience. *Aging Med (Milton)*. 2019;2(3):147-156. Published 2019 Sep 8. doi:10.1002/agm2.12080

181 - Nathiya D, Raj P, Singh P, et al. Frailty Predicting Health-Related Quality of Life Trajectories in Individuals with Sarcopenia in Liver Cirrhosis: Finding from BCAAS Study. *J Clin Med*. 2023;12(16):5348. Published 2023 Aug 17. doi:10.3390/jcm12165348

182 - Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Reprint--preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Phys Ther*. 2009;89(9):873-880.

183 - Artru F, Miquet X, Azahaf M, Labreuche J, Ntandja Wandji LC, Sergent G, Nobécourt A, Toumelin P, Lassailly G, Dharancy S, Ernst O, Mathurin P, Louvet A. Consequences of TIPSS placement on the body composition of patients with cirrhosis and severe portal hypertension: a large retrospective CT-based surveillance. Aliment Pharmacol Ther. 2020 Nov;52(9):1516-1526. doi: 10.1111/apt.16080. Epub 2020 Sep 15. PMID: 32931618.

184 - Liu J, Ma J, Yang C, Chen M, Shi Q, Zhou C, Huang S, Chen Y, Wang Y, Li T, Xiong B. Sarcopenia in Patients with Cirrhosis after Transjugular Intrahepatic Portosystemic Shunt Placement. Radiology. 2022 Jun;303(3):711-719. doi: 10.1148/radiol.211172. Epub 2022 Mar 15. PMID: 35289658.

185 - Jahangiri Y, Pathak P, Tomozawa Y, Li L, Schlansky BL, Farsad K. Muscle Gain after Transjugular Intrahepatic Portosystemic Shunt Creation: Time Course and Prognostic Implications for Survival in Cirrhosis. J Vasc Interv Radiol. 2019 Jun;30(6):866-872.e4. doi: 10.1016/j.jvir.2019.01.005. Epub 2019 Apr 30. PMID: 31053265.

186 - Pang N, Zhao C, Li J, Li L, Yang X, Yang M, Wu Z, Feng D. Body mass index changes after transjugular intrahepatic portosystemic shunt in individuals with cirrhosis. Nutrition. 2021 Apr;84:111095. doi: 10.1016/j.nut.2020.111095. Epub 2020 Nov 30. PMID: 33571910.

187 - Trotter JF, Suhocki PV, Rockey DC. Transjugular intrahepatic portosystemic shunt (TIPS) in patients with refractory ascites: effect on body weight and Child-Pugh score. Am J Gastroenterol. 1998 Oct;93(10):1891-4. doi: 10.1111/j.1572-0241.1998.00544.x. PMID: 9772050.

188 - Plauth M, Schütz T, Buckendahl DP, Kreymann G, Pirlich M, Grüngreiff S, Romaniuk P, Ertl S, Weiss ML, Lochs H. Weight gain after transjugular intrahepatic portosystemic shunt is associated with improvement in body composition in malnourished patients with cirrhosis and hypermetabolism. J Hepatol. 2004 Feb;40(2):228-33. doi: 10.1016/j.jhep.2003.10.011. PMID: 14739092.

189 - Nolte W, Wirtz M, Rossbach C, Leonhardt U, Buchwald AB, Scholz KH, Ramadori G. TIPS implantation raises leptin levels in patients with liver cirrhosis. Exp Clin Endocrinol Diabetes. 2003 Oct;111(7):435-42. doi: 10.1055/s-2003-44291. PMID: 14614651.

190 - Body composition changes after transjugular intrahepatic portosystemic shunt in patients with cirrhosis. Montomoli J, Holland-Fischer P, Bianchi G, Grønbæk H, Vilstrup H, Marchesini G, Zoli M. Body composition changes after transjugular intrahepatic portosystemic shunt in patients with cirrhosis. *World J Gastroenterol* 2010; 16(3): 348-353 [PMID: 20082481 DOI: 10.3748/wjg.v16.i3.348]

191 - Allard JP, Chau J, Sandokji K, Blendis LM, Wong F. Effects of ascites resolution after successful TIPS on nutrition in cirrhotic patients with refractory ascites. Am J Gastroenterol. 2001 Aug;96(8):2442-7. doi: 10.1111/j.1572-0241.2001.04051.x. PMID: 11513188.

192 - Holland-Fischer P, Vilstrup H, Frystyk J, Nielsen DT, Flyvbjerg A, Grønbaek H. The IGF system after insertion of a transjugular intrahepatic porto-systemic shunt in patients with liver cirrhosis. Eur J Endocrinol. 2009 Jun;160(6):957-63. doi: 10.1530/EJE-08-0971. Epub 2009 Mar 31. PMID: 19336524.

193 - Holland-Fischer P, Nielsen MF, Vilstrup H, Tønner-Nielsen D, Mengel A, Schmitz O, Grønbaek H. Insulin sensitivity and body composition in cirrhosis: changes after TIPS. Am J Physiol Gastrointest Liver Physiol. 2010 Aug;299(2):G486-93. doi: 10.1152/ajpgi.00375.2009. Epub 2010 May 20. PMID: 20489042.

194 - Thomsen KL, Sandahl TD, Holland-Fischer P, Jessen N, Frystyk J, Flyvbjerg A, Grønbæk H, Vilstrup H. Changes in adipokines after transjugular intrahepatic porto-systemic shunt indicate an anabolic shift in metabolism. Clin Nutr. 2012 Dec;31(6):940-5. doi: 10.1016/j.clnu.2012.04.001. Epub 2012 Apr 27. PMID: 22541535.

195 - Qi X, Jia J, Bai M, Guo X, Su C, García-Pagán JC, Han G, Fan D. Transjugular Intrahepatic Portosystemic Shunt for Acute Variceal Bleeding: A Meta-analysis. J Clin Gastroenterol. 2015 Jul;49(6):495-505. doi: 10.1097/MCG.0000000000000205. PMID: 25127113.

196 - Salerno F, Cammà C, Enea M, Rössle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology. 2007 Sep;133(3):825-34. doi: 10.1053/j.gastro.2007.06.020. Epub 2007 Jun 20. Erratum in: Gastroenterology. 2007 Nov;133(5):1746. PMID: 17678653.

197 - de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022. Epub 2021 Dec 30. Erratum in: J Hepatol. 2022 Jul;77(1):271. doi: 10.1016/j.jhep.2022.03.024. PMID: 35120736; PMCID: PMC11090185.

198 - Fagiuoli S, Bruno R, Debernardi Venon W, Schepis F, Vizzutti F, Toniutto P, Senzolo M, Caraceni P, Salerno F, Angeli P, Cioni R, Vitale A, Grosso M, De Gasperi A, D'Amico G, Marzano A; AISF TIPS Special Conference. Consensus conference on TIPS management: Techniques, indications, contraindications. Dig Liver Dis. 2017 Feb;49(2):121-137. doi: 10.1016/j.dld.2016.10.011. Epub 2016 Oct 29. PMID: 27884494.

199 - Giri S, Anirvan P, Chaudhary M, Tripathy T, Patel RK, Rath MM, Panigrahi MK. Impact of nutritional status on the outcome of transjugular intrahepatic portosystemic shunt in

patients with cirrhosis: a systematic review. Br J Radiol. 2024 Feb 2;97(1154):331-340. doi: 10.1093/bjr/tqad065. PMID: 38276881.

200 - Wijarnpreecha K, Werlang M, Panjawatanan P, Kroner PT, Cheungpasitporn W, Lukens FJ, Pungpapong S, Ungprasert P. Association between sarcopenia and hepatic encephalopathy: A systematic review and meta-analysis. Ann Hepatol. 2020 May-Jun;19(3):245-250. doi: 10.1016/j.aohep.2019.06.007. Epub 2019 Jul 13. PMID: 31422030.

201 - Hey P, Chapman B, Wong D, Gow P, Testro A, Terbah R, Sinclair M. Transjugular intrahepatic portosystemic shunt insertion improves muscle mass but not muscle function or frailty measures. Eur J Gastroenterol Hepatol. 2023 Sep 1;35(9):997-1003. doi: 10.1097/MEG.0000000000002592. Epub 2023 Jun 16. PMID: 37395688.

202 - Padilha DMH, Mendes MCS, Takahashi MES, Lascala F, Silveira MN, Pozzuto L, Carrilho LAO, Guerra LD, Moreira RCL, Branbilla SR, Ramos CD, Carvalheira JBC. Subcutaneous adipose tissue radiodensity: An emerging risk factor for severe COVID-19. Nutrition. 2024 Dec;128:112561. doi: 10.1016/j.nut.2024.112561. Epub 2024 Aug 20. PMID: 39277984.

203 - Iida S, Matsumoto Y, Toyozumi T, Otsuka R, Shiraishi T, Morishita H, Makiyama T, Nishioka Y, Yamada M, Hirata A, Hayano K, Ohira G, Kano M, Matsubara H. High Subcutaneous Adipose Tissue Radiodensity Predicts Poor Prognosis in Patients With Gastric Cancer. Cancer Diagn Progn. 2024 Nov 3;4(6):754-761. doi: 10.21873/cdp.10392. PMID: 39502618; PMCID: PMC11534057.