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EDITORIAL

Quick and easy assessment of sarcopenia in cirrhosis: Can ultrasound be the solution?

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Abstract

Cirrhosis is frequently associated with sarcopenia, with reported rates of over 80% in patients with decompensated alcohol-related liver disease. Sarcopenia negatively impacts the prognosis of cirrhotic patients and affects the response to treatment of patients with hepatocellular carcinoma (HCC). For these reasons, identifying an easy-to-perform method to assess sarcopenia in is a key element in the optimization of care in this patient population. Assessment of muscle mass by computed tomography is considered the standard of care for the diagnosis of sarcopenia, but exposure to radiation and high costs limit its application in this setting, especially for repeated assessments. We believe that ultrasound, a cheap and harmless technique also used for HCC screening in cirrhotic patients, could have an expanding role in the diagnosis and follow-up of sarcopenia in these patients.

Key Words: Sarcopenia; Ultrasound; Cirrhosis; Hepatocellular carcinoma; Computed tomography

Core Tip: Cirrhosis is frequently associated with sarcopenia, which negatively impacts the prognosis of cirrhotic patients and affects the response to treatment of patients with hepatocellular carcinoma (HCC). For these reasons, identifying an easy-to-perform method to assess sarcopenia in is a key element in the optimization of care in this patient population. We believe that ultrasound, a cheap and harmless technique also used for HCC screening in cirrhotic patients, could have an expanding role in the diagnosis and follow-up of sarcopenia in these patients.

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INTRODUCTION

Cirrhosis is frequently associated with sarcopenia, with reported rates of over 80% in patients with decompensated, alcohol-related cirrhosis[1]. Various pathogenetic mechanisms contribute to muscle wasting in these patients, such as altered protein metabolism, resulting in reduced levels of circulating branched chain amino acids[2] and decreased protein synthesis, increased autophagy, proteolysis, and mitochondrial oxidative dysfunction in the skeletal muscle due to hyperammonemia[3,4]. Chronic systemic inflammation[5], reduction in circulating testosterone levels[6,7], and physical inactivity[8,9] are other factors contributing to sarcopenia in patients with advanced liver disease. Sarcopenia negatively affects the prognosis of cirrhotic patients and the response to treatment in patients with hepatocellular carcinoma (HCC). For these reasons, identifying an easy-to-perform method to assess sarcopenia is a key element in the optimization of care in this patient population. Assessment of muscle mass by computed tomography (CT) is considered the standard of care for the diagnosis of sarcopenia, but exposure to radiation and high costs limit its application in this setting, especially for repeated assessments. We believe that ultrasound (US), a cheap and harmless technique also used for HCC screening in cirrhotic patients, may have an expanding role in the diagnosis and follow-up of sarcopenia in these patients.

DEFINITION OF SARCOPENIA

Sarcopenia is a progressive and generalized skeletal muscle disorder mainly defined by two parameters: Muscle mass and muscle strength. Low muscle strength is the key characteristic of probable sarcopenia, whereas a diagnosis of sarcopenia can be confirmed only after detection of low muscle quantity and quality[10]. Moreover, reduced physical performance is indicative of severe sarcopenia[10], which is associated with an increased likelihood of adverse outcomes including falls, fractures, disability, and mortality[10]. Loss of skeletal muscle mass and function commonly occurring with advancing age is classified as primary sarcopenia, but many other factors can cause or contribute to the development of secondary sarcopenia[10]. Systemic diseases, especially those characterized by inflammatory processes, are one of the leading causes of secondary sarcopenia[11]. Physical inactivity and inadequate energy or protein intake are also involved in the development of sarcopenia[11].

Sarcopenia is also common in overweight and obese patients[11,12], where the loss of muscle mass and function can be favored by chronic low-grade inflammation, increased oxidative stress, insulin resistance, sedentary lifestyle, and a higher incidence of comorbid chronic diseases that may negatively impact muscle metabolism[13]. Several lines of evidence show that sarcopenic obesity represents a strong and independent risk factor for frailty, comorbidities, and mortality, especially among the elderly[14,15].

PREVALENCE AND ROLE OF SARCOPENIA ACROSS LIVER DISEASES

Sarcopenia in metabolic dysfunction-associated steatotic liver disease patients

Sarcopenia is closely associated with metabolic dysfunction-associated steatotic liver disease (MASLD), the most common cause of chronic liver disease in Western countries[16,17]. Patients with sarcopenic MASLD are generally older and more frequently female[18]. Sarcopenia has been suggested to increase the risk of progression of liver fibrosis, and therefore its early recognition may play an important role in preventing the development of cirrhosis[19-21]. Petta *et al*[22] showed that MASLD-sarcopenic patients have more severe liver fibrosis compared with those without. Moreover, the co-occurrence of MASLD and sarcopenia is associated with higher mortality, suggesting that sarcopenia may play a role in increasing the risk of cardiovascular diseases, metabolic disorders, and physical disability in this group of patients[23,24].

Sarcopenia and cirrhosis

Sarcopenia affects between 30% to 70% of cirrhotic patients[25], with higher rates reported in men[26,27]. The etiology of cirrhosis plays a relevant role in the development of sarcopenia. The highest prevalence of sarcopenia can be found in

patients with alcohol-associated cirrhosis, with a prevalence of over 80% in alcohol-related decompensated cirrhosis[1,28]. Alcohol consumption affects muscle mass leading to muscle autophagy, inhibition of proteasome activity and a decrease in insulin-like growth factor 1[29]. Sarcopenia can be both a cause and a consequence of complications of cirrhosis. Ascites may favor muscle loss through anorexia, reduced mobility, and frequent hospitalizations[30]. On the other hand, reduced muscle mass is an independent risk factor for hepatic encephalopathy[31,32] and is linked to an increased risk of decompensation[33].

In cirrhosis, sarcopenia also negatively impacts quality of life[34], increases the risk of infection[35], and prolongs the duration of hospitalizations[36]. Additionally, several studies show that a diagnosis of sarcopenia in cirrhotic patients is associated with an increased risk of falls, fractures, acute-on-chronic liver failure, and death[37-39]. Indeed, a recent systematic review and metanalysis of 22 studies including 6965 cirrhotic patients showed that the risk of death was 2.6 times higher in patients with sarcopenia[27]. Low muscle density has been shown to predict mortality even in patients with compensated cirrhosis[33,40], and sarcopenic obesity is associated with a higher incidence of sepsis-related death [41]. The presence of sarcopenia prior to liver transplantation can significantly increase the length of hospital and intensive care unit (ICU) stay[42,43] and worsens the overall prognosis of these patients[44].

Sarcopenia and HCC

Up to 30%-40% of HCC patients are affected by sarcopenia at the time of diagnosis, at least partially because of the pro-inflammatory state triggered by the altered tumor microenvironment[45]. As sarcopenia influences the response to surgical, locoregional, and systemic treatments, its timely recognition is essential. In patients who undergo liver resection or liver transplantation, tackling sarcopenia reduces sepsis-related complications and length of ICU stay, and decreases patient mortality[46]. In patients treated with thermal ablation, sarcopenia has been linked to a reduced overall survival (OS) and to a higher risk of HCC recurrence[47]. A worse prognosis and high rate of progression has been also described for HCC patients treated with transarterial chemoembolization[48].

Sarcopenia also appears to impact the response to systemic treatments. Scheiner *et al*[49] showed that sarcopenia is associated with worse OS (6.5 months *vs* 20.9 months), progression-free survival (5.8 months *vs* 8.3 months) and objective response rate (22% *vs* 39%) in patients treated with atezolizumab-bevacizumab. Sarcopenic patients treated with sorafenib were subject to a higher drug exposure and increased dose-limiting toxicities *vs* non-sarcopenic patients[50]. In patients treated with lenvatinib, Dong *et al*[51] showed that sarcopenia is an independent prognostic factor of a shorter OS. Sarcopenia might also predict drug toxicity and poor tolerance to lenvatinib[52]. Based on the above findings, an adequate evaluation and diagnosis of sarcopenia in patients with HCC is likely to improve their prognosis.

CURRENT METHODS FOR SARCOPENIA DIAGNOSIS

Although the diagnosis of sarcopenia involves both a functional and quantitative assessment of muscle mass, current research is mainly directed at finding an objective and reproducible method to measure muscle mass. CT imaging currently represents the gold standard to quantify skeletal muscle. Muscle mass is conventionally reported as skeletal mass index (SMI), calculated as the total skeletal muscle area at the level of L3 normalized for height[26]. SMI is the only parameter for which cut-off values for the diagnosis of sarcopenia have been validated, < 50 cm for men and < 39 cm for women[10,26,53]. Alternatively, the psoas muscle index at L3 has been identified as an alternative to SMI, although it shows low accuracy in cirrhotic patients[54]. However, CT scan is not an adequate method to serially follow the improvement or deterioration of muscle mass over time, because of high radiation exposure[55]. For this reason, body composition is assessed with CT scans only when these are performed for other reasons, as in the setting of HCC.

Dual-energy x-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and bioelectrical impedance analysis (BIA) are currently available alternatives, albeit various limitations should be considered. DXA is a costly, radiation-dependent technique influenced by body mass index and fluid retention. MRI is highly accurate but expensive and with restricted availability in most settings. BIA is population and device-dependent and is also affected by fluid retention. When technology-based devices (BIA, DXA, MRI or CT) are not available or feasible, anthropometric measures could be used to quantify skeletal muscle mass, at the expense of test sensitivity and reproducibility[56].

THE ROLE OF US IN SARCOPENIA DIAGNOSIS

US is an accurate and reliable technique, with high reproducibility for the assessment of muscle size[57,58]. Furthermore, abdominal US is used to screen cirrhotic patients for HCC semiannually, in accordance with guidelines of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases[59,60]. Therefore, the availability of US in virtually all cirrhotic patients, its non-invasiveness and independence of exposure to X-rays, make it an appealing tool for the initial diagnosis and follow-up of sarcopenia in cirrhosis[61], also in clinical studies.

The use of US in muscle assessment has been specifically explored in patients with cirrhosis. It must be noted that most studies included patients with a mild or moderate reduction in liver function (Child Pugh classes A and B) due to the high impact of ascites on the evaluation of psoas muscle by US[62-64]. Furthermore, HCC patients are generally excluded by these studies due to neoplastic cachexia which is considered a confounding factor.

The anatomical site that best represents total skeletal muscle mass has not yet been defined. The rectus femoris (RF) could be a possibility as it is exposed to an earlier age-related decline than other sites such as the biceps femoris[65]. Most

studies evaluating sarcopenia in cirrhotic patients through US used the measurement of large muscles in the upper and lower limbs because of their ease of identification and lesser susceptibility to fluid retention[63]. In fact, ascites can influence the sonic window, especially when examining the muscles of the abdominal wall or psoas[63]. The same issue can be encountered in patients with obesity, a condition that, due to the rising global prevalence, is going to be very frequent in patients with cirrhosis[63]. Another aspect that needs to be defined is the US parameter to be used in muscle mass assessment. Thickness and cross-sectional area of the muscle show similar results as those of DXA, CT, and MRI and may be used to confirm the presence of muscle mass depletion[66]. Echo intensity is a measure of muscle composition in terms of fatty infiltration and presence of fibrous tissue[67]. Indeed, US machines are increasingly equipped with software that could be useful in qualitative analysis of the muscle, defining its microvasculature or stiffness[68-70]. Two-dimensional shear wave elastography of the RF is another qualitative parameter proposed for the assessment of lean mass using US. The measurement of stiffness with this method was feasible in all patients and correlated with liver frailty index (LFI) in a study that involved 44 outpatients with cirrhosis. In addition, RF thickness inversely correlated with LFI [70].

Other key aspects that require standardization are the type of probe that should be employed, the anatomical sites of measurement, the patient's position during the examination, the probe direction and pressure exerted on the muscle, and the parameters that should be measured[68]. A linear probe with a frequency of 5-12 MHz is usually preferred, except for the psoas muscle, for which the use of a convex probe with a frequency of 3.5-5 MHz appears to be more adequate[63].

Despite the lack of standardization, there is growing evidence on the use of US to assess sarcopenia in cirrhotic patients. A recent review evaluating 17 studies assessed the role of US in the diagnosis of sarcopenia in older adults, and showed that US is accurate for the assessment of muscles size, especially when the evaluation is targeted at the quadriceps femoris[57]. In a prospective study including 159 cirrhotic outpatients, Tandon *et al*[71] demonstrated that the combination of body mass index and US-measured thigh muscle thickness was able to identify sarcopenic patients, in both genders, with the same efficacy as CT[71]. This implies an evident advantage in terms of increased screening feasibility and serial assessment to monitor the effectiveness of nutritional interventions[71]. Of note, even in the context of cirrhosis and obesity, the assessment of lean mass through US has been demonstrated to be well-correlated with SMI calculated from CT[72]. Similarly, when LFI or subjective global assessment were employed as references for the assessment of muscle function, a robust correlation with US measurements (*i.e.*, the antero-posterior diameter of the RF, rectus abdominis thickness) was found[70,73].

Besides demonstrating a strong correlation with the reference gold standard, the assessment of lean mass using US also correlates with various clinical outcomes. For example, rectus abdominis thickness predicts survival in a study that included a small group of cirrhotic patients, and both US-SMI and US-psoas to height ratio were significantly related to hospitalization in patients with decompensated liver cirrhosis[73,74].

CONCLUSION

Despite the above outlined limitations and the limited amount of data in large series, the wide availability of the instrument, its ease of application, and especially the possibility of repeated monitoring on the same patient makes US assessment of lean mass in patients with cirrhosis an attractive area of interest for future study.

FOOTNOTES

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