



Editorial

Muscle abnormalities in cirrhosis: Calling for more strength in evaluation and prevention



*Gira el mon i torna al Born**.

During the last five years, particular attention has been given to skeletal muscle abnormalities in patients with cirrhosis, since these carry independent prognostic value on clinical outcome. Skeletal muscle abnormalities include sarcopenia, which is defined as a progressive and generalized loss of skeletal muscle mass, strength and function, and myosteatosis, which means excessive and pathological fat accumulation in muscles.

Traditionally, sarcopenia was a major issue in geriatric medicine, since there is a functional decline of muscle due to aging, with a 0.5% of annual loss of muscle mass. Sarcopenia is not only relevant in terms of capacity of maintaining a normal physical activity, but it also has a negative impact on the immune response, increasing the likelihood of infections [1]. However, it is estimated that sarcopenia occurs in up to 70% of patients with advanced cirrhosis, regardless of age, leading to a higher risk of decompensation, of infections, and worsening the waiting list and post-liver transplantation outcomes [2]. On the other hand, sarcopenia is further enhanced when patients are admitted to hospital due to complications of cirrhosis, thus closing a vicious circle where liver failure further enhances muscle loss and vice versa. Interestingly, sarcopenia is also extremely frequent in patients with NASH, underscoring the lack of correlation between an excessive body weight and loss of muscle mass (sarcopenic obesity) [3].

From this perspective, the Chief Editors of Digestive and Liver Disease have chosen to highlight the topic by publishing in this issue of DLD several papers focusing on sarcopenia in advanced chronic liver disease. The first is a comprehensive review by Ebadi et al. (a) summarizing the current knowledge regarding skeletal muscle abnormalities in cirrhosis. The authors discuss the clinical impact of sarcopenia and myosteatosis on the prognosis of patients with cirrhosis, from a liver transplantation (LT) perspective, considering existing, as well as novel, potential therapeutic strategies to improve nutritional status and sarcopenia in these patients [4]. Rendina et al. (b) in their Letter to the Editor underline the increasing age of liver transplant candidates and the deleterious effect of therapies such as large volume paracentesis enhancing protein-loss in patients with refractory ascites, which calls for interventions aimed at decreasing malnutrition. In the liver transplant setting, as well as in all patients with advanced cirrhosis, they suggest that providing nutritional advice and support together with adequate counseling on physical-activity might

represent an opportunity for positive point-of-care intervention. A positive response to such therapeutic intervention might help in distinguishing which candidates should be prioritized among those with poor pre-transplant outcome indicators [5]. In addition, the authors hypothesize that transjugular intrahepatic portosystemic shunt (TIPS) could improve nutritional status in patients with refractory ascites waiting for LT. This is in keeping with some studies documenting that sarcopenia in patients with cirrhosis can be improved/reversed after TIPS [6]. However we are still far from predicting in which patients will sarcopenia improve after TIPS or, on the contrary, those in whom it might worsen, in the context of deterioration of liver function [7].

Therefore, it is possible that quantifying these muscle abnormalities might ameliorate prognostication in patients awaiting LT. If proven correct, this may even lead to modifications in current organ allocation policy, and perhaps decrease the rates of futile LT. Since the validation of Model for End-Stage Liver Disease (MELD) score to predict mortality in patients undergoing TIPS placement, there have been concerns regarding its prognostic accuracy in stratifying the severity of patients with end-stage liver disease. When used in clinical scenarios different from TIPS placement, it soon become evident that some complications of cirrhosis, not explored by the MELD score, could provide additional prognostic information [8]. This is well illustrated by MELD-Na for LT and more recently by the CLIF-SOFA score for acute-on-chronic liver failure (ACLF) [9] that have demonstrated better performance as compared to MELD score alone in predicting survival and are increasingly used in clinical practice.

Although sarcopenia has been unanimously recognized as a complication affecting mortality and morbidity in patients with cirrhosis, we still need more data to demonstrate that a modified prognostic model, integrating muscle abnormalities is superior to current prognostic indexes. In 2015, Montano-Loza proposed the MELD-sarcopenia score [10] in order to add accuracy to MELD alone in LT, but this failed validation in a subsequent study in an independent cohort [11], which generated significant debate. Indeed, the robustness of the data of both works suffered from being based on retrospective studies, leading to significant risk of selection bias on the studied populations. These limitations are also present in the work of Lattanzi et al. in this issue of DLD (c). These authors propose a comprehensive index including hepatic encephalopathy, myosteatosis, and sarcopenia, in addition to the MELD score. However, some of their conclusions are

not entirely supported by evidence. For instance, unexpectedly, deleting hepatic encephalopathy (the heaviest prognostic factor) from the model did not result in a significant decrease in accuracy for 3- and 6-month mortality prediction, which may derive from relatively low numbers regarding sample size, prevalence of encephalopathy and deaths on follow-up. On the other hand, they observed that deleting myosteatosis from the model resulted in a significant loss in prognostic accuracy, suggesting that sarcopenia and myosteatosis might influence prognosis by independent mechanisms.

Despite requiring further validation by adequately conducted, large, prospective studies, the proposal of integrating sarcopenia and myosteatosis in a prognostic model for patients entering a waiting list for LT is of clinical relevance and timely on the light of the above-mentioned studies. However, translating these findings into clinical practice would probably require simpler and reliable non-invasive tools to quantify skeletal muscle abnormalities, its evolution and response to therapeutic intervention. At present, the direct quantification of skeletal muscle mass requires cross-sectional imaging with CT as gold standard [12]. Although CT scan is frequently performed in cirrhosis, it is far from ideal as a screening tool due to its non-negligible irradiation risks. Interestingly, some simple tests such as the Liver Frailty Index (LFI), which assess residual physical function (and therefore may be considered kind of a surrogate of muscle abnormalities in cirrhosis), has been shown to be a strong predictor of survival that adequately correlates with mortality in the waiting list for LT [13]. The current article by Hari and coworkers represents another attempt at more directly assessing muscle abnormalities at point-of-care. **(d)** They used standard ultrasonography, which is safe and largely available, for measuring the psoas muscle diameter in patients with decompensated liver cirrhosis as an index of sarcopenia. Interestingly, their findings show an association of this parameter and the incidence of decompensation events and mortality on follow-up. Despite the authors recognize limitations such as sub-optimal reproducibility, applicability and operator-dependence, this represents an interesting approach to incorporate the prognostic value of muscular abnormalities into daily clinical practice.

To conclude, the prognostic value of skeletal muscle impairment in patients with cirrhosis is increasingly recognized by the hepatological community. The main efforts are now focusing on easily and objectively quantifying sarcopenia and myosteatosis and on how we can integrate this knowledge in routine clinical practice. More studies are required to establish, first, solid evidence on the prognostic value of muscle abnormalities along the course of chronic liver disease due to different etiologies, and second, whether reverting sarcopenia by tailored nutritional and lifestyle intervention is associated with an improved outcome, or if there is a point of no-return beyond which such intervention would be ineffective. If all this is proven, we would still need simpler and safe ways of assessing sarcopenia at point-of-care and demonstrate that the information provided is independent and more accurate than the LFI in assessing prognosis. So, we foresee an increasing interest on this topic of clinical research in hepatology and hope that this will lead to a clinical benefit for our patients, not only in terms of patient stratification for demanding interventions, but also in terms of better survival and quality of life through preventative strategies based on nutritional and lifestyle intervention.

There was a time where nutrition was almost the only therapeutic tool available to hepato-gastroenterologists. With the abundance of specific and increasingly effective therapies, nutrition

and lifestyle have been much neglected, as evidenced in hepatology by the NASH epidemic. Is it time for a comeback?

*Catalan dictum indicating that what we were looking for all over the world was in fact close to us.

Conflict of interest

None declared.

References

- [1] Wilson D, Jackson T, Sapey E, Lord JM. Frailty and sarcopenia: the potential role of an aged immune system. *Ageing Res Rev* 2017;36:1–10.
- [2] Kim HY, Jang JW. Sarcopenia in the prognosis of cirrhosis: going beyond the MELD score. *World J Gastroenterol* 2015;21(25):7637–47.
- [3] De Fre CH, De Fre MA, Kwanten WJ, Op de Beeck BJ, Van Gaal LF, Francque SM. Sarcopenia in patients with non-alcoholic fatty liver disease: is it a clinically significant entity? *Obes Rev* 2019;20(2):353–63.
- [4] Berzigotti A, Albillos A, Villanueva C, Genesca J, Ardevol A, Augustin S, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: the SportDiet study. *Hepatology* 2017;65(4):1293–305.
- [5] Stirnimann G, Ebadi M, Tandon P, Montano-Loza AJ. Should sarcopenia increase priority for transplant or is it a contraindication? *Curr Gastroenterol Rep* 2018;20(11):50.
- [6] Tsién C, Shah SN, McCullough AJ, Dasarathy S. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic shunt. *Eur J Gastroenterol Hepatol* 2013;25(1):85–93.
- [7] Praktikno M, Clees C, Pigliacelli A, Fischer S, Jansen C, Lehmann J, 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.
- [8] Lucidi C, Ginanni Corradini S, Abraldes JG, Merli M, Tandon P, Ferri F, et al. Hepatic encephalopathy expands the predictivity of model for end-stage liver disease in liver transplant setting: evidence by means of 2 independent cohorts. *Liver Transplant* 2016;22(10):1333–42.
- [9] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69(2):406–60.
- [10] Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, Baracos VE, Sawyer MB, Pang JX, et al. Inclusion of sarcopenia within MELD (MELD-sarcopenia) and the prediction of mortality in patients with cirrhosis. *Clin Transl Gastroenterol* 2015;6:e102.
- [11] van Vugt JLA, Alferink LJM, Buettner S, Gaspersz MP, Bot D, Darwish Murad S, et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: a competing risk analysis in a national cohort. *J Hepatol* 2018;68(4):707–14.
- [12] Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. *Liver Transplant* 2017;23(5):625–33.
- [13] Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017;66(2):564–74.

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