Editorial

Determinants of prognosis in cirrhosis: a new outlook

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The metanalysis by Tantai and collaborators highlights the role of sarcopenia in cirrhosis by demonstrating that the presence of muscular alterations is independently related with a mortality (HR 2.61) (1). Sarcopenia is confirmed as a condition with high prevalence in patients with cirrhosis (37.5%), being more representative in males than females (41.9% *vs.* 37.8%) and in subjects with alcoholic etiology (49.6%) or with more advanced degree of liver disease (Child Pugh C 46.7%). Interestingly, authors demonstrate that sarcopenia was associated with mortality in subjects with MELD <15 or ≥15 (HR 2.34) as well evaluating only on studies that excluded patients with hepatocellular carcinoma (HCC), risk of mortality was similar to that of the main analysis (2.35) (1).

Cirrhosis is a devasting disease with a well-recognized social and healthcare burden. Mortality is even higher if the course of disease is characterized by clinically significant portal hypertension and/or primary liver cancer. MELD represents a widely used scoring system able to assess the severity of liver disease or mortality risk of the patient as well as for patient's allocation for liver transplantation.

Recently, role and weight of some new, clinical, and non-biochemical indicators for the assessment of disease severity and prognosis, such as muscle alterations, frailty, and spontaneous portosystemic shunts (SPSS), have been described. For example, with regard to muscle alterations and frailty, recently published guidelines of the American Association for the Study of Liver Disease (2) pay particular attention to the correlation and interplay between malnutrition, sarcopenia and frailty. These guidelines provide an interesting point of view, tackling the same problem from three different angles. Indeed, malnutrition results from an imbalance (in deficiency or in excess) of nutrients causing a series of adverse effects on tissue/body form or function, and/or different clinical outcomes leading to a series of adverse physical effects such as frailty or sarcopenia. Frailty is a condition characterized by a decreased physiologic reserve and an increased vulnerability to health stressors, this is a definition borrowed from the geriatric sphere. This condition reflects a series of clinical manifestations following an impaired muscle contractile activity common in cirrhosis leading to a decreased physical function, decreased functional performance, and disability. Sarcopenia is a well-known progressive and generalized condition characterized by a diffuse skeletal muscle loss associated with an increase of adverse outcomes including falls, fractures and consequently disability, and even mortality. Both frailty and sarcopenia are closely related to hepatic encephalopathy (HE), a frequent and serious complication of cirrhosis causing a full spectrum of nonspecific neurological and psychiatric manifestations, ranging from a not overt form, the minimal HE (MHE) to a more complex form characterized by a complete alteration of consciousness (overt HE). HE has a high prevalence and a significant impact on both the patient and the caregiver, is related to an increased risk of falls and mortality (3,4). The pathophysiological background that supports the correlation between muscle depletion and HE has its cornerstone in the role played by the muscle in ammonia metabolism and trafficking. Ammonia, being increased because of the inability of the liver in removing ammonia through urea synthesis due to liver failure and/or

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the presence of porto-systemic shunts, is therefore involved both in the pathogenesis of cognitive impairment and in terms of prognosis. A healthy skeletal muscle may act as an effective player with a compensatory role in ammonia clearance through glutamine-synthase, which metabolize ammonia into glutamine. As a consequence, this muscle depletion may favour an increase in ammonia levels and finally HE development. Moreover, recently, Tranah and collaborators carried on a perspective study aimed to assess the association between blood ammonia and the risk of adverse outcomes in 754 patients with cirrhosis. Authors conclude that ammonia represent a key determinant that helps to predict hospitalizations, development of liver-related complications and die (5).

Furthermore, muscular alterations of patients with minimal or overt before and after Transjugular Intrahepatic Portosystemic Shunt (TIPS) at CT scan have been studied by our group. We were able to demonstrate the presence of a putative relationship between TIPS and an amelioration of muscle wasting and HE independently of liver function (6). Moreover, TIPS seemed to modify also adipose tissue. Indeed, the improvement both of subcutaneous adipose tissue and sarcopenia and/or myosteatosis are related to an amelioration in cognitive impairment without relationship with liver function. These evidences suggest that adipose tissue may play a role in the inter-organ ammonia trafficking (7). Under this light, also the presence both of muscular alterations and/or visceral fat, should be taken strongly in account during the workout of patients candidates to TIPS.

Therefore, an integrated approach, consisting of an optimization of the nutritional and dietary regimen, associated with sustainable physical activity, may, in addition to specific medical therapy for any other complications of an advanced liver disease, significantly improve patient outcomes both for the nutritional and muscular issues, and for prevent HE or falls and, more in general, aiming to ameliorate the prognosis.

SPSS are frequent in decompensated cirrhotic patients (8-11). For years, SPSS have been considered as protective factors because of their theoretically capability to reduce portal pressure and so portal hypertension-related complications. Recently, more and more studies showed that they are markers of advanced portal hypertension and that they are not able to decompress portal venous system (9-11). On the contrary, by shunting the blood from the portal to systemic circulation, they contribute to decrease hepatocyte perfusion as documented by the reduction of liver volume in patients with large SPSS (9). These factors promote neo-angiogenesis in the splanchnic circulation maintaining the mechanisms causing the hyperdynamic circulation state. As a consequence, they are implicated both in liver dysfunction and portal hypertension. Nardelli *et al.* showed that SPSS, dependently on the type and size, are associated to portal hypertensive complications especially HE, gastric variceal bleeding, and portal vein thrombosis (9). In fact, their presence is associated with a 2.3-fold increase in the risk of any event of decompensation (12). Moreover, SPSS have been found independently associated with mortality or liver transplantation (10,11). Radiological embolization of the shunt is a treatment option for persistent/recurrent HE and gastric variceal bleeding and it leads also to an improvement in liver function tests (13,14), liver volume, and, in patients without cirrhosis, an improvement in survival (14). This is why, the search of SPSS or their closure in particular situations, is now recommended as a part of the workup of the cirrhotic patient (15).

It appears therefore fundamental to approach at new and emerging clinical determinants of advanced liver disease, such as sarcopenia and myosteatosis and SPSS, from a different point of view, in which some various new factors could add prognostic value to the known and well-established biochemical ones. Indeed, not only the presence of cirrhosis, even complicated by decompensation or development of HCC, but also the occurrence of sarcopenia, malnutrition or SPSS could exert a major role to identify patients at risk for decompensation or death. The management of patients with advanced liver disease should be approached under this entire panorama, aiming to detect a well-defined subgroup of very high-risk patients in which, after an accurate clinical, biochemical and instrumental assessment, a "non-classical" management could be added to the standard (15). New prognostic tools able to combine these significant clinical (presence and severity of HE and/or muscular alterations), radiological (spontaneous/iatrogenic shunts) and biochemical variables (MELD, ammonia) to identify and promptly treat these extremely at-risk patients represent an interesting new horizon. Further multicenter, collaborative, perspective studies are therefore needed to assess this possibility and to validate the new tools that will be proposed.

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