Letter to the Editor

JOURNAL OF HEPATOLOGY

Gut liver muscle brain axis: A comprehensive viewpoint on prognosis in cirrhosis

To the Editor:

We read with interest the paper by Tantai *et al.* in which the authors conclude that sarcopenia was highly and independently associated with a higher risk of mortality in patients with cirrhosis.[1]

Cirrhosis is a well-known devasting disease with a heavy social and healthcare burden. Mortality in patients suffering from advanced liver disease is higher if the course of disease is complicated by clinically significant portal hypertension. The model for end-stage liver disease (MELD) score is widely used to assess the severity of liver disease, its mortality and to help prioritise patients for liver transplantation. In recent years, the relationship between muscular alterations and hepatic encephalopathy (HE) has been deeply studied. The pathophysiological background supporting the relationship between muscle depletion and HE starts from the involvement of muscle in ammonia metabolism and trafficking. Ammonia plays a central role in the pathogenesis of cognitive impairment in cirrhosis, being increased because of the inability of the liver to remove ammonia through urea synthesis due to liver failure and/or the presence of porto-systemic shunts. Skeletal muscle may play a compensatory role in ammonia clearance through glutamine-synthase, which metabolizes ammonia into glutamine. Consequently, muscle depletion may favour ammonia accumulation and finally HE development.[2] We recently described the relationship between muscular alterations and HE, both minimal and overt.[3] In the same study, survival was significantly lower in malnourished patients compared to patients without sarcopenia. Moreover, the accuracy of MELD in predicting 3- and 6-month mortality may be improved by considering muscular alterations. Indeed, a model considering the above parameters may more accurately classify over 30% of patients.[4] Therefore, HE and muscle alterations could be used to improve the determination of prognosis in patients with cirrhosis. Herein, we report some data on patients with cirrhosis prospectively followed by our unit, in which a comprehensive assessment of liver disease as well as of mental status has been performed. The presence of sarcopenia was evaluated accordingly to skeletal muscle index obtained by CT scan. Occurrence of HE episodes and mortality have also been recorded.

One hundred and fifty one patients with cirrhosis (M/F 107/44), age 59.5±11.6 years, with a prevalence of viral aetiology (75/50%) were followed up for a mean period of 12.7±10.1 months. Severity of cirrhosis was evaluated by Child-Pugh Class (A/B/C: 40/80/31) and MELD score (13.8±5). Sarcopenia was present in 84 patients (56%) and previous history of HE in 51 (34%) patients. Death occurred in 59 (39%) patients during follow-up, while overt HE occurred in 53 (35%) of patients. The presence of sarcopenia (29% *vs.* 7%, p <0.001), previous HE (28% *vs.* 6%, p <0.001), or HE during follow-up (25% *vs.* 9%, p = 0.005) were associated with a higher mortality rate. In order to establish the relative role of the variables significantly associated with mortality, a multivariate analysis using Cox Regression including in the model an index of severity of liver disease (MELD) and the presence of sarcopenia and previous HE was performed. Co-presence of previous HE and sarcopenia were independently associated with mortality (HR 2.56, p = 0.0056, 95% CI 1.3-5), thus improving the prognostic value of MELD alone (HR 1.1, p <0.001, 95% CI 1-1.16). Moreover, the incidence of death was significantly higher in patients with sarcopenia and previous HE (log rank p = 0.009), as shown in Fig. 1.

While sarcopenia can be easily assessed with an appropriate imaging technique (*e.g.* CT), the objective evaluation both of presence and grading of HE remains more challenging. However, these results confirm the important role of muscle alterations and HE as concomitant and important co-factors for mortality in patients with cirrhosis.

It is therefore crucial to look at the emerging clinical determinants of cirrhosis, such as muscle alterations, from a different perspective, in which some various new factors could add prognostic value to the oldest and most well-established ones. Indeed, not only the presence of a severe liver disease, or a previous history of minimal/covert HE, or iatrogenic portosystemic shunts, but also sarcopenia, nutritional deficit or spontaneous portosystemic shunts could play a major role. Patients with cirrhosis should be considered under this complex and whole panorama, aiming to identify a well-defined subgroup of very high-risk patients, in which other factors with a deeper clinical and instrumental assessment and a consequent "non classical" management should be adopted.[5] The future could involve validation of new prognostic tools able to combine these robust clinical (HE or sarcopenia), radiological (spontaneous/iatrogenic

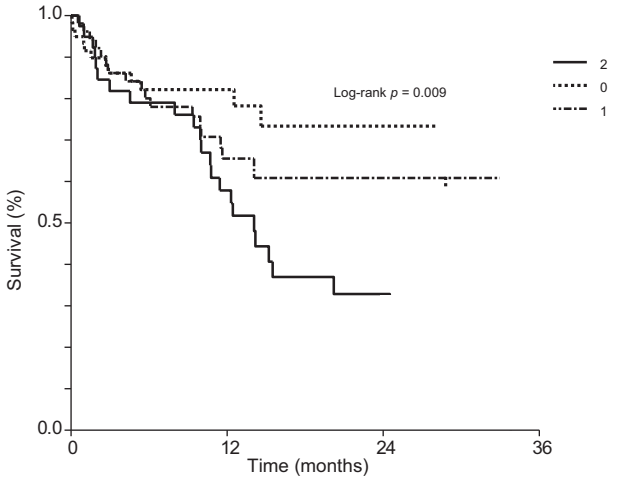

Fig. 1. Cumulative survival in patients without sarcopenia and without previous HE (0), with sarcopenia or previous HE (1) and with sarcopenia and previous HE (2). HE, hepatic encephalopathy.

Received 20 December 2021; received in revised form 10 January 2022; accepted 11 January 2022; available online xxx
https://doi.org/10.1016/j.jhep.2022.01.003

shunts) and biochemical (MELD) variables with the aim of identifying and promptly treating extremely high-risk patients.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Lorenzo Ridola: conceptualization and manuscript draft, data analysis, critical revision for important intellectual content, final approval
Stefania Gioia: data analysis, critical revision for important intellectual content
Jessica Faccioli: data collection
Oliviero Riggio: critical revision for important intellectual content
Silvia Nardelli: data analysis, critical revision for important intellectual content, final approval.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.01.003.

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Lorenzo Ridola*
Stefania Gioia
Jessica Faccioli
Oliviero Riggio
Silvia Nardelli
Department of Translational and Precision Medicine, "Sapienza" University of Rome, Italy
*Corresponding author. Address: Department of Translational and Precision Medicine, "Sapienza" University of Rome, Viale dell'Università 37, Rome, Italy.
E-mail address: lorenzo.ridola@uniroma1.it (L. Ridola)