Digestive and Liver Disease 51 (2019) 1508–1512

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

The additive value of sarcopenia, myosteatosis and hepatic encephalopathy in the predictivity of model for end-stage liver disease

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ARTICLE INFO

Article history:
Received 13 May 2019
Accepted 5 September 2019
Available online 7 October 2019

Keywords:
Hepatic encephalopathy
Model for end-stage liver disease
Myosteatosis
Sarcopenia

ABSTRACT

Background: Since the use of the Model for End-Stage Liver Disease (MELD) score for establishing the prognosis of cirrhotic patients has been introduced, questions have been raised whether complications of liver cirrhosis would provide additional information. Myosteatosis, sarcopenia and hepatic encephalopathy (HE) are frequent in cirrhosis and may affect prognosis.

Aim of the study was analyzing if these factors are independently related to survival and may improve the accuracy of MELD.

Methods: 249 cirrhotics that underwent abdominal CT-scan were enrolled. For each patient, information about previous episodes of HE and muscle alterations were obtained. Patients were followed until transplantation or death.

Results: History of HE, MELD, sarcopenia and myosteatosis were independently associated with mortality. The MELD-Sarco-Myo-HE score added accuracy to the MELD score alone for 6- and 3-months mortality. By removing HE, as the only not quantifiable parameter of the model, no relevant decrease in accuracy for 6- and 3-months mortality detection was observed.

Conclusions: The accuracy of MELD in predicting 3- and 6-months mortality may be improved by considering the muscle alterations. A model considering the above parameters may classify more accurately over 30% of the patients.

1. Introduction

The use of an accurate, objective and reproducible scoring system for severity of liver disease is highly important for clinical management of patients with advanced liver disease. The laboratory-based model for end-stage liver disease (MELD) score has been developed and validated to predict mortality in patients with portal hypertension undergoing placement of transjugular intrahepatic portosystemic shunts (TIPS) [1]. Subsequently, this score was used in patients with a broad spectrum of liver diseases showing a discriminatory power to predict short-term mortality regardless of TIPS placement [2].

However, since the use of MELD as a predictor of short-term mortality in patients with cirrhosis has been introduced, questions have been raised whether complications of liver cirrhosis may provide additional prognostic information [3,4]. In fact, despite its known predictive value [5,6], there are patients whose survival cannot be accurately estimated by the MELD score [7] with many authors proposing different score systems in order to effectively predict short-term survival [8–11].

In this field, a frequently reported drawback of the MELD score is the lack of nutritional parameters leading to an underestimation of the mortality risk of cirrhotic patients affected by malnutrition. It is well known that the presence of low muscle mass (sarcopenia) and the fatty infiltration of muscle (myosteatosis) are well known negative prognostic factors in patients with liver cirrhosis [12–15].

Furthermore, a recent study found that the implementation of the MELD score with sarcopenia (MELD-Sarcopenia score) had an higher predictive accuracy for short-term mortality compared to

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https://doi.org/10.1016/j.dld.2019.09.004
1590-8658/

the MELD score alone [9]. While the external validation of this score failed to identify the superiority of MELD-Sarcopenia in comparison to the MELD score alone in the 3-months mortality; developing a score, inclusive of the history of hepatic encephalopathy (HE) resulted in a higher predictive rate in the short-term mortality [16].

Indeed, HE is another factor not included in the MELD score that has been related to a worse prognosis in cirrhosis [17–20]. In a recent study by Lucidi et al, the prognostic relevance of HE was highlighted in a large series of cirrhotic patients leading to the proposal of a MELD-HE score [8].

Thus, despite the awareness that the MELD score is still not the "ideal" method for the detection of short-term mortality in patients with cirrhosis, the role of sarcopenia, myosteatosis and HE in the implementation of the MELD scores in its efficiency, is still unclear.

In this scenario, we performed a study aimed at analyzing if the above factors are independently related to survival and may be used to improve the accuracy of the MELD score.

2. Patients and methods

2.1. Study cohort

The study retrospectively analyzed demographic, clinical and biochemical data prospectively collected in cirrhotic patients from our center between 2009 and 2013 that underwent an abdominal CT scan for any clinical reason (surveillance of focal liver lesions, vascular study and pre-transplant evaluation). Exclusion criteria were advanced neoplastic diseases including hepatocellular carcinoma (HCC) out of the Milan criteria; severe extrahepatic diseases; concomitant neurological diseases and ages <18 and >70 years. Demographic, clinical, biochemical parameters and MELD score were recorded at inclusion for each patient. Patients were observed until LT or death.

2.1.1. Hepatic encephalopathy detection

A detailed clinical history about previous episodes of overt HE was obtained for each patient. The patients were qualified as "HE+" if a previous episode of overt HE ≥ grade II (according to West Heaven criteria) was documented by a previous hospitalization. The cut-off for grade II HE was the presence of an acute confusional syndrome with clear disorientation in time upon neurological examination. In case of a less severe degree of HE (grade I, or covert HE) the patient was qualified as having a negative history of overt HE ("HE−").

2.1.2. Nutritional assessment

The quantitative analysis of muscle mass for each patient was obtained using SliceOmatic V4.2 software (Tomovision, Montreal, Quebec, Canada) [21,22]. The muscle areas of the psoas, paraspinal and abdominal wall (including rectus abdominis, transverse abdominis, and internal and external oblique) at L3 slice were identified and carefully marked in order to obtain a specific tissue demarcation. Skeletal muscle was identified and quantified by HU thresholds of −29 to +150 [22]. All CT images were analyzed by two observers (A.P., S.D.) in order to reduce the variability in muscle areas demarcation. With these specific HU thresholds, measurements of the muscle mass were not influenced by the presence of ascites. Cross-sectional areas (cm^2) were automatically computed by summing tissue pixels and multiplying by pixel surface area. Muscle cross-sectional area was normalized for height to obtain the skeletal muscle index (SMI) in cm^2/m^2. The cut-offs for the identification of sarcopenic patients are those proposed and previously validated in cirrhotic patients (<50 cm^2/m^2 for men and <39 cm^2/m^2 for women) [23].

For myosteatosis the mean muscle attenuation in HU for the entire muscle area at L3 was considered. The cut-offs of muscle attenuation previously used in cirrhotic patients, were applied to identify patients with myosteatosis, specifically <41 HU in patients with a BMI < 24.9 and <33 HU in those with a BMI ≥ 25 [12,24].

2.2. Statistical analysis

The MELD score was calculated using the standard formula: $11.2 \times \ln$ (INR) + $9.57 \times \ln$ (creatinine, in mg per deciliter) + $3.78 \times \ln$(bilirubin, in mg per deciliter) + 6.43, with a lower limit of 1 for all variables. Patient demographics and baseline biochemical parameters were tabulated and compared using descriptive statistics. Formal assessment of relationships between baseline measurements and mortality rate were done through the Gray test, given that transplant is a competing risk for death. At multivariate analyses, we used proportional sub-distribution hazards from Fine's and Gray's models. The sub-distribution hazard ratios (sHR) were reported in all tables. Increases in the C-index and the net reclassification index (NRI) were used to assess improvements in discrimination after the addition of markers to the MELD. The indexes were estimated at 3 and 6 months. The NRI gives roughly the proportion of patients, misclassified by the MELD alone, and correctly classified by taking into account additional predictors. In all cases, the optimal number of points were determined by rounding and scaling logarithms of sub-distribution hazard ratios as estimated through the corresponding Fine's and Gray's regression model. Data were analyzed using R (R development core team) v3.4.0.

3. Results

3.1. Study cohort

Three-hundred-forty-five cirrhotic patients were observed in our centre between 2009 and 2013. Of these, 60 patients did not undergo CT scan, 21 were affected by HCC out of the Milan criteria, 2 had extrahepatic neoplasia and 13 were >70 years old. A total of 249 cirrhotic patients were enrolled in the study: 172 outpatients and 77 hospitalized patients. The follow-up was similar in the two groups (15.7 ± 13 months in the outpatients and 14.8 ± 13 months in the hospitalized; p = 0.4).

The majority of the enrolled patients were male (76%), the mean age was 60 ± 8 years and the median MELD score at enrollment was 14.4 ± 5.4, the mean follow-up was 92.3 ± 49.9 months. The main demographic, clinical and biochemical characteristics at the basal evaluation are shown in Table 1.

3.2. Analysis of mortality

During the 6-months follow-up, 37 (15%) patients died and 30 (14%) underwent transplantation. Several clinical and biochemical variables potentially associated with mortality were submitted to univariate and multivariate analysis. HE + status, biologic MELD score, sodium MELD score, history of ascites, sarcopenia and myosteatosis were significantly associated with overall mortality (Table 2). Similar results were obtained from the analysis of 3-months and 6-months mortality. When the above parameters were included in a multivariate analysis, HE+ (sHR 3.439; 97.5% CI 1.898–6.231; p < 0.001), MELD (sHR 1.052; 97.5% CI 1.003–1.104; p = 0.038), sarcopenia (sHR 1.866; 97.5% CI 1.076–3.236; p = 0.026) and myosteatosis (sHR 1.981; 97.5% CI 1.109–3.538; p = 0.021) resulted as independent predictors of mortality.

3.3. MELD score optimization

The AUC of MELD alone in the 6-month mortality prediction obtained from our cohort was 70.2% (97.5%CI: 58.9–81.3).

Table 1
Demographic, clinical, and biochemical characteristics of patients at the enrollment.

Variables	Overall patients N = 249
Age, years	60 ± 8
Sex, males	190 (76%)
Main origin of liver disease n (%)	
Alcohol	60 (24%)
Viral	142 (57%)
Alcohol + virus	19 (8%)
Nash	8 (3%)
Others	21 (8%)
Gastroesophageal varices, n (%)	165 (66%)
Ascites, n (%)	124 (50%)
HCC, n (%)	112 (45%)
Biological MELD score	14.4 ± 5.4
Sarcopenia, n (%)	109 (44%)
Myosteatosis, n (%)	135 (54%)
SMI (cm^2/m^2)	51.5 ± 29.4
Mean muscle attenuation (HU)	35.9 ± 8.9
History of HE, n (%)	104 (42%)
Follow-up, months	15.1 ± 17.6

Values are expressed in mean ± standard deviation; Abbreviations: HCC: hepatocellular carcinoma; MELD: model of end-stage liver disease; SMI: skeletal muscle index; HU: Hounsfield unit; HE: hepatic encephalopathy.

Considering the presence of sarcopenia and myosteatosis together with HE, we obtained the following score (MELD-Sarco-Myo-HE score):

$$0.05 \times \text{MELD} + 1 \times (\text{HE} = \text{“yes”}) + 0.5 \times (\text{sarcopenia} = \text{“yes”}) + 0.5 \times (\text{myosteatosis} = \text{“yes”})$$

The AUC of MELD-Sarco-Myo-HE score in the 6-month mortality prediction obtained from our cohort was 80.6% (97.55%CI: 74.1–87.4) (Fig. 1). This score added accuracy to the MELD score with a 1/2 NRI of 0,352 (97.5%CI: 0.073–0.520, p < 0.001). Similar results were found for 3-months mortality.

When the continuous variables of muscle attenuation and SMI were used, the score found was: 0.05 MELD + HE − 0.05 attenuation − 0.025 SMI, with a AUC of 82.6% (76.7–88.8) similar to that described in the manuscript by using categorical variables. Sensitivity was 86%, Specificity 69% at the optimal cut-off of −1.71.

In addition, we wanted to detect if there were any differences in accuracy if we removed the variable “HE” from the score, considering the MELD-Sarco-Myo score:

$$0.05 \times \text{MELD} + 0.5 \times (\text{sarcopenia} = \text{“yes”}) + 0.5 \times (\text{miosteatosi} = \text{“yes”})$$

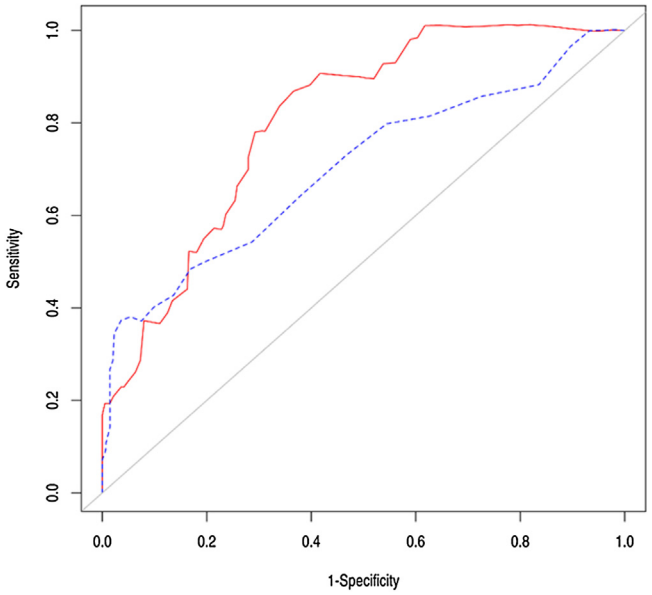

Fig. 1. ROC curves of MELD-Sarco-Myo-HE score and MELD-score for 6-months mortality.
The MELD score is expressed in dashed line (AUROC 0.81 vs. 0.70; 1/2 NRI 35% p < 0.001).

The AUC of MELD-Sarco-Myo score in the 6-month mortality prediction obtained from our cohort was 78.6% (97.5%CI: 0.692–0.873).

The score obtained by using continuous variables of muscle attenuation and SMI without HE was: 0.05 MELD −0.075 MYO −0.025 SMI, presenting an AUC of 81.1% (73.4–88.6) similar to that described in the manuscript by using categorical variables. Sensitivity was 73% and Specificity 78% at the optimal cut-off of −2.82. We found that the MELD-Sarco-Myo score was not statistically different in accuracy in comparison with MELD-Sarco-Myo-HE for short-term mortality (p = 0.286) (Fig. 2).

The MELD-Sarco-Myo score was more accurate in comparison to the MELD score for 6-months mortality (1/2 NRI 0.330; 97.5%CI: 0.163–0.504, p < 0.001) (Fig. 3). Similar results were found for 3-months mortality.

Finally, in order to obtain the simpler score without losing accuracy, we remove the variable Myo, considering the MELD-Sarco score:

$$0.05 \times \text{MELD} + 0.5 \times (\text{sarcopenia} = \text{“yes”})$$

Table 2
Univariate analysis of risk factors associated with overall mortality.

	Alive during follow-up (n = 184)	Death during follow-up (n = 65)	sHR	97.5%CI	p-value
Sex (M/F)	43/141	16/49	1.10	0.50–2.43	0.81
Age (yrs)	56.3 ± 7.7	54.7 ± 11.5	0.97	0.93–1.01	0.14
Aetiology (virus/alcohol/alcohol + virus/NASH/other)	101/48/10/6/19	41/12/8/2/2	1.50	0.45–4.98	0.51
MELD biological	13.8 ± 4.7	16.1 ± 6.6	1.10	1.06–1.14	<0.001
MELD Sodium	15.3 ± 5.9	19.8 ± 6.9	1.13	1.09–1.17	<0.001
Gastroesophageal varices (no/yes)	66/118	18/47	1.05	0.53–2.08	0.89
Ascites (no/yes)	104/80	21/44	3.07	1.50–6.25	0.002
HCC (no/yes)	96/88	41/24	0.74	0.38–1.43	0.37
Previous HE (no/yes)	128/56	17/48	4.06	1.97–8.38	0.001
Diabetes (no/yes)	126/57	47/18	0.62	0.28–1.37	0.24
Sarcopenia (no/yes)	112/72	28/37	3.03	1.47–6.21	0.003
Myosteatosis (no/yes)	97/87	17/48	3.44	1.58–7.48	0.002

Values are expressed in mean ± standard deviation; Abbreviations: NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; MELD: model of end-stage liver disease; HE: hepatic encephalopathy.

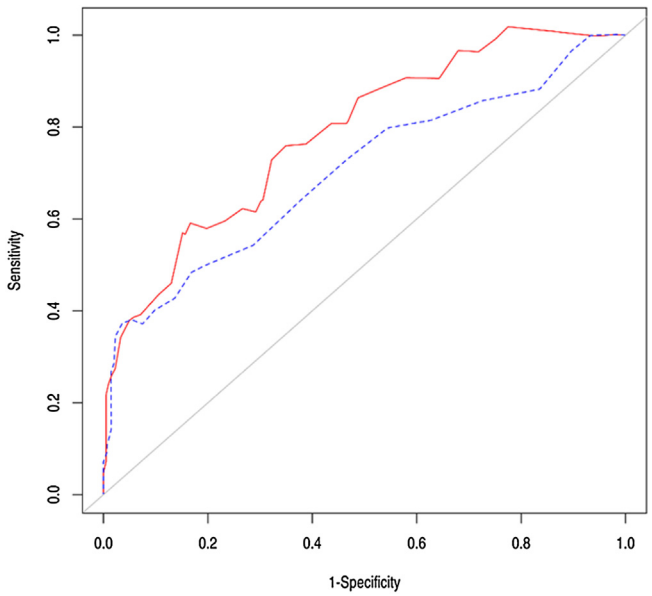

Fig. 2. ROC curve of MELD-Sarco-Myo score and MELD-score for 6-months mortality.
MELD score is expressed in dashed line (AUROC 0.81 vs. 0.78; 1/2 NRI 35% p = 0.286).

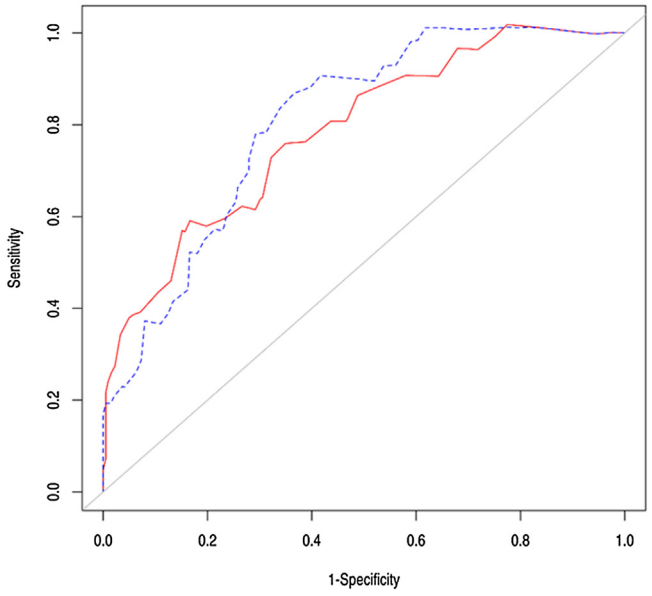

Fig. 3. ROC curve of MELD-Sarco-Myo-HE score and MELD-Sarco-Myo for 6-months mortality.
MELD-Sarco-Myo-HE score is expressed in dashed line (AUROC 0.78 vs. 0.70; 1/2 NRI 33% p < 0.001).

However, this time we observed a significant loss in accuracy in comparison with the MELD-Sarco-myo score (1/2 NRI −0.329; 97.5%CI: −0.469 to 0.165; p = 0.013).

4. Discussion

Since the MELD score was introduced in clinical practice, questions have been raised about the accuracy of this score in the identification of the sickest patients and if complications of liver cirrhosis, not subtended in the MELD score, could provide additional prognostic information [3,4]. In this field, the debate is still ongoing concerning the possible role of nutritional status and HE history in the MELD score [8,9,16]. Sarcopenia is recognized as a negative prognostic index in liver cirrhosis in terms of mortality and morbidity [13,25,26]. However, while one study found an additional accuracy in the MELD-sarcopenia score [9] a recent analysis failed to validate this score in an external cohort [16]. Recently, some authors showed the negative impact of myosteatosis in liver disease, rising interest in the quality of muscle mass [27]. In our study we confirm the importance of sarcopenia as a predictor of mortality in cirrhotic patients and, furthermore, we found an independent prognostic value of myosteatosis in this setting. In fact, when we tried to simplify the score by removing the myosteatosis, we found a significant loss in accuracy suggesting that sarcopenia and myosteatosis are two independent negative prognostic factors in cirrhotic patients and these muscle abnormalities often do not co-exist in the same patient. Indeed, while sarcopenia refers to muscle quantity, the presence of myosteatosis refers to an alteration in the quality of muscle mass due to the increased proportion of intermuscular and intramuscular fat. In our series, we found that sarcopenia was present in 44% of patients, myosteatosis in 54% of patients and only 30% of patients presented both these alterations. The fact that these two conditions do not co-exist and have independent prognostic values, has emerged in previous series were sarcopenia and myosteatosis resulted in having an independent negative effect on survival and HE development in cirrhotic patients [12,27].

On the other hand, it is well known that HE is another frequent complication of liver cirrhosis that represents a negative prognostic factor for morbidity and mortality [17,18]. While in the Child-Pugh score and in the originally developed Child-Turcotte score the presence of HE and of nutritional parameters such as albumin levels (indirect sign of malnutrition) or a subjective definition of malnutrition were included, the MELD score, in order to be more objective, does not consider these two entities with the risk to underestimate mortality in the sickest patients. Our study confirms the impact of HE on mortality in patients with cirrhosis. Our group already showed the great impact of the history of HE in the short and long-term mortality in patients with cirrhosis and we proposed, the MELD-HE as a predictor of mortality in these patients [8]. However, knowing all too well that an ideal score should be reproducible, easily applicable and as objective as possible, we recognize that the history of HE should sometimes waiver objectivity. Moreover, the kind of HE could be of relevance (i.e. time from the hospitalization for HE to evaluation, grade of HE at hospitalization, the cause of HE etc.). For these reasons, even if we are aware of the importance of HE, we notice that if we added more objective parameters such as sarcopenia and myosteatosis to the MELD score, we can remove the history of HE from the score with no significant loss of accuracy.

This is probably due to the link between HE and malnutrition [28]. Indeed, we have already shown that malnutrition represents a risk factor for the onset of HE [15,29] and this relationship may be due to the same metabolic alterations.

This study has some limitations, in fact, it is a monocentric and retrospective study and for this reason, more studies and external validation of data are needed. Moreover, enrolling only patients with a CT scan can lead to a selection biasand analyzing data of enrolled patients and those without a CT scan, we did not find any differences in terms of age, gender, etiology, previous episodes of HE and MELD score.

We decided to use categorical values for sarcopenia and myosteatosis in order to use this score also when nutritional assessment is performed with other techniques such as psoas thickness, dual energy x-ray absorptiometry, bioelectrical impedance analysis and ultrasound [21,30–32]. In order to confirm our data, we performed the same analysis using continuous variables for sarcopenia and myosteatosis, obtaining similar results.

In conclusion, the accuracy of MELD in predicting 3- and 6-months mortality may be improved by considering the previous

history of HE and muscle alterations detected by CT scan. A model considering the above parameters may more accurately classify more than 30% of the patients. History of HE is important but the accuracy of the model without this possibly biased parameter is not reduced significantly.

Conflict of interest

None declared.

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