Cirrhosis

Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography

François Durand[1,2,*], Sophie Buyse[1], Claire Francoz[1,2], Cédric Laouénan[3,4], Onorina Bruno[5], Jacques Belghiti[6], Richard Moreau[1,2], Valérie Vilgrain[2,5], Dominique Valla[1,2]

[1]Hepatology and Liver Intensive Care Unit, Hospital Beaujon, Clichy, France; [2]INSERM U773, Centre de Recherche Biomédicale Bichat Beaujon CRB3, France; [3]Biostatistics Department, Hospital Bichat, Paris, France; [4]INSERM UMR 738, Université Paris Diderot, Sorbonne Paris Cité, France; [5]Department of Radiology, Hospital Beaujon, Clichy, France; [6]Hepatobiliary Surgery and Liver Transplantation, Hospital Beaujon, Clichy, France

Background & Aims: Waiting-list mortality in patients with cirrhosis and a relatively low MELD score is a matter of concern. The aim of this study was to determine whether a marker of muscle waste could improve prognostication.

Methods: A pre-MELD cohort (waiting time-based allocation; n = 186) and a MELD-era cohort (n = 376) were examined. At evaluation, transversal psoas muscle thickness (TPMT) was measured on a computed tomography (CT) image at the level of the umbilicus. In the pre-MELD cohort, TPMT/height (mm/m) and the MELD score were entered in univariate and multivariate models to predict mortality after registration. Applicability of pre-MELD findings was tested in the MELD-era.

Results: In the pre-MELD cohort, the MELD score and TPMT/height were significantly associated with mortality. The discrimination of a score combining MELD and TPMT/height (MELD-psoas) was 0.84 (95% CI, 0.62–0.95). In the MELD-era, TPTM/height was significantly associated with mortality, independent of the MELD and MELD-Na scores. There was a 15% increase in mortality risk per unit decrease in TPMT/height. The discrimination of MELD-psoas score (0.82; 95% CI, 0.64–0.93) was superior to that of the MELD score and similar to that of the MELD-Na score. In patients with refractory ascites, mortality was significantly higher when TPMT/height was <16.8 mm/m (42% *vs.* 9%, *p* = 0.02).

Conclusions: TPMP/height on CT at the level of the umbilicus, an objective marker of muscle waste, may be predictive of mortality in cirrhotic patients, independent of the MELD and MELD-Na scores. It may help to better assess the prognosis of patients with refractory ascites.

Introduction

Optimizing prognostic scores is a central issue in the management of cirrhosis. The MELD score, based on the objective values of bilirubin, creatinine, and INR has been widely adopted as the reference score for prioritization of candidates for transplantation [1,2]. According to a "sickest-first" policy, patients with the highest MELD score and the highest risk of early mortality are prioritized for transplantation. The usefulness of the MELD score to predict outcome in cirrhosis has been illustrated beyond the scope of transplantation [3]. The MELD score, however, is not a perfect prognostic tool and some cirrhotic patients may be misclassified. For instance, it has been shown that persistent ascites and low serum sodium identify cirrhotic patients with a low MELD score who are at high risk of early mortality without transplantation [4–6]. Serum sodium was found to have a prognostic value independent of that of the MELD score [7,8]. Addition of serum sodium to the MELD score improved prognostic accuracy, patients with low serum sodium being at higher risk of mortality [8].

Several studies using different markers have shown that poor nutritional status in candidates for transplantation may be associated with an increased incidence of early post-transplant sepsis and prolonged stay in the intensive care [9–12]. However, objective assessment of nutritional status in cirrhotic patients remains a challenging issue. A number of factors including water retention, ascites, and decreased protein synthesis represent potential biases with usual markers. Therefore, whether poor nutritional status predicts increased mortality, independent of the MELD score in patients with cirrhosis is still debated with discordant results according to different markers. A recent study has suggested that sarcopenia estimated by cross sectional area of several muscles including psoas on computed tomography (CT) or magnetic resonance images (MRI) at the L3 vertebral level could be an independent predictor of mortality in candidates for transplantation [13]. Another recent study exploring assessment of body composition on a CT scan transverse section at the L3-L4

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level with a software differentiating adipose and skeletal muscle areas, and computing the corresponding surfaces was conducted in liver transplant candidates [14]. This study has suggested that decreased muscle mass corrected for height, but not adipose tissue, may be predictive of post-transplant survival [14]. This objective approach in the assessment of muscle mass is attractive. However, measurement of the surface of different groups of muscles needs computation, is relatively complex and hardly generalizable. The aim of this study was to measure the effect of axial and transversal psoas muscle thickness on CT scan at the level of the umbilicus in predicting mortality in patients with cirrhosis on the waiting list for liver transplantation.

Patients and methods

Study population and design

Data on all consecutive adult patients with cirrhosis registered for deceased donor liver transplantation in our tertiary referral center were obtained from 2002 to 2011. The study population corresponded to 2 consecutive cohorts. The first cohort (pre-MELD cohort) consisted of patients listed for transplantation between February 2002 and February 2007, a period during which allocation was based on waiting time. The second cohort (MELD-era cohort) consisted of patients listed for transplantation from March 2007 to December 2011. March 2007 corresponded to the implementation of the MELD score-based allocation policy in France [15]. These two periods were defined in order to determine whether the findings observed in a first cohort, where waiting list mortality globally reflected the natural history of cirrhosis, could be applicable in the MELD-era.

In pre-MELD and MELD-era cohorts, patients listed for cirrhosis and small hepatocellular carcinoma (HCC) were included along with patients without HCC in order to cover a large spectrum of disease severity. Indeed, a substantial proportion of patients with HCC have a low MELD score at registration. According to our local policy, all patients with HCC had tumors meeting the Milan criteria [16]. As from March 2007, allocation policy in patients with HCC was based on both the MELD score and tumor status as described previously [17]. In patients with HCC and a high MELD score, prioritization was essentially based on the MELD score. On the opposite, patients with HCC and a low MELD score received extra-points to reach a maximum score (equivalent to a MELD score of 40) 24 months after registration. In between, there was a continuum between the MELD score and HCC. The higher the MELD score the lower the extra points for HCC [17]. Patients who had to be removed from the waiting list due to tumor progression over the Milan criteria or improvement were censored at the time of removal. Patients listed for living donor transplantation or multiple organ transplantation, HIV-infected patients and patients with any prioritization corresponding to MELD exceptions [17] were excluded. For all calculations, we only used the physiological MELD score.

The study protocol conformed to the ethical guidelines of the 1975 declaration of Helsinki and was approved by the local ethics committee.

Measurement of psoas muscle thickness on CT scan: Image analysis

Axial and transversal psoas muscle thickness was measured in all patients based on numerically stored abdominal CT scans performed for the purpose of pre-transplant evaluation. Psoas muscle thickness was selected among other anthropometric markers because psoas can be easily identified on a CT scan. Additionally, psoas is a deep muscle which, in contrast to parietal muscles, may not be directly affected by abdominal distension in patients with ascites.

CT scan measurements and laboratory data were obtained during pre-transplant evaluation, within a maximum of 5 consecutive days. The interval between pre-transplant evaluation and listing for transplantation was of less than 3 weeks. Measurements were performed on a single axial CT scan image corresponding to the level of the umbilicus. Axial psoas muscle thickness (APMT) corresponded to the largest diameter of psoas muscle on an axial view. Transversal psoas muscle thickness (TPMT) corresponded to the diameter of psoas muscle perpendicular to the axial diameter (Fig. 1). All measurements were performed on the right psoas muscle. Psoas muscle thickness was normalized to stature by division by height.
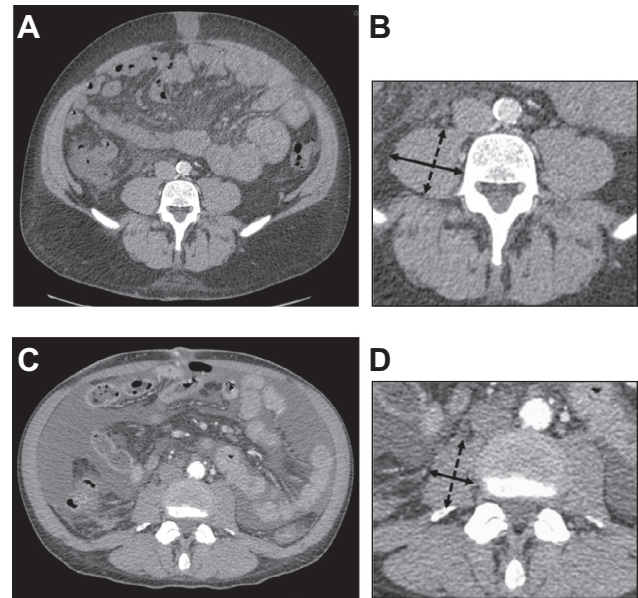

Fig. 1. Measurement of psoas muscle thickness at the level of the umbilicus on a CT scan image. (A) Axial computed tomography scan image at the level of the umbilicus in a patient with alcohol abuse-related cirrhosis, a MELD score of 23, transversal psoas muscle thickness/height of 26 mm/m, no refractory ascites and who was transplanted 6 months after registration. (B) Details on measurements of transversal psoas muscle thickness (continuous line) and axial psoas muscle thickness (dotted line). (C) Axial computed tomography scan image at the level of the umbilicus in a patient with hepatitis C virus-related cirrhosis, a MELD score of 9, transversal psoas muscle thickness/height of 13 mm/m, refractory ascites and who died on the waiting list 2.7 months after listing. (D) Details on measurements of transversal psoas muscle thickness (continuous line) and axial psoas muscle thickness (dotted line).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were presented as percentages. Inter-operator reproducibility of the measurement of psoas muscle thickness on CT scan was assessed using the intraclass correlation coefficient (ICC) and its 95% confidence interval (CI). In univariate analysis, patient's characteristics were compared using the Student's t test or Mann-Whitney test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Cumulative survival curves were determined according to the Kaplan-Meier method and compared with the log-rank test. Univariate analysis was performed in the pre-MELD cohort with a Cox proportional hazards model to describe the relationships between waiting list mortality and risk scores (the MELD score and TPMT/height) and possible confounders (gender, ethnicity, cause of cirrhosis, hepatocellular carcinoma, refractory ascites, age, and BMI). Variables with $p <0.20$ in univariate analysis were entered in a multivariate adjusted Cox proportional hazards model with a backward selection procedure and a significance level of $p <0.05$. A new score (MELD-psoas) was derived from parameter estimates given by Cox model in the pre-MELD cohort including the MELD score and TPMT/height. The discrimination of risk scores was assessed by the overall C index, defined as a natural extension of the receiver operating characteristic area to survival analysis and its 95% CI [18]. Observed rates with their 95% CI and predicted rates of waiting list mortality were computed to assess the calibration of the risk scores. The optimal cut point of TPMT/height to discriminate waiting list mortality was estimated by the Youden index. To study the effect of TPMT/height on the relative risk of waiting list mortality in the MELD-era cohort, a generalized additive model with smoothing splines adjusted on the MELD score was used. Correlations between scores and continuous variables were assessed using the Pearson correlation coefficient. Data were analyzed using the SAS® 9.3 software (SAS institute, Cary, NC, USA) and the function concordance index of the R® package survcomp [19].