Prevalence and prognosis of Computed-Tomography defined sarcopenia in Tunisian cirrhotic patients

Prévalence et pronostic de la sarcopénie définie par tomodensitométrie au cours de la cirrhose en Tunisie

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Abstract

Introduction: Sarcopenia is an underdiagnosed and understudied complication of cirrhosis, especially in patients not undergoing liver transplantation.

Aim: To evaluate the prevalence and prognostic impact of radiological sarcopenia in non-transplanted cirrhotic patients.

Methods: Longitudinal retrospective study including cirrhotic patients explored by an abdominal CT scan, over a period of 6 years, in a single gastroenterology department in Tunisia. Sarcopenia was defined according to transversal psoas muscle thickness normalized to height (TPMT/h) in the sagittal CT slice. Two groups were defined: Group 1 with sarcopenia (TPMT/h <16.8mm/m); and Group 2 without sarcopenia (TPMT/h ≥16.8mm/m).

Results: Seventy patients were included (mean age=62 years). The mean MELD score was 12.81 and the mean TPMT/h of 13.56 mm/m. Forty-four patients were sarcopenic (63%). When included, the 2 groups' baseline characteristics were comparable except for women predominance and refractory ascites in group 1. After an average of 21-month follow-up, sarcopenia was associated with a higher number of complications per patient (p=0.013) and a longer average hospital stay duration per patient (p=0.001). Overall survival was significantly decreased in sarcopenic patients (p=0.035). Survival rates at 6 months, 1 year, and 2 years were respectively 42%, 30%, and 24% in Group 1 versus 67%, 40%, and 27% in Group 2. Sarcopenia was an independent factor of mortality in multivariate analysis (OR=2.5;95% IC [1.02-6.16]; p=0.045).

Conclusion: Sarcopenia is frequent and an independent poor prognostic factor in cirrhosis. TPMT/h is an easy and often available method for sarcopenia diagnosis.

Mots-clés : sarcopénie, malnutrition, cirrhose, tomodensitométrie, pronostic, mortalité

Résumé

Introduction : La sarcopénie est une complication sous-évaluée chez le cirrhotique avec une prévalence et un impact pronostique inconnus en particulier chez le cirrhotique non transplanté.

Objectifs : Evaluer la prévalence et le pronostic de la sarcopénie chez les cirrhotiques non transplantés

Méthodes : Étude rétrospective longitudinale incluant, tous les cirrhotiques d'un centre tunisien de gastroentérologie, et ayant bénéficié d'une tomodensitométrie abdominale sur une période 6 ans. La sarcopénie était définie radiologiquement par une épaisseur du muscle psoas rapportée à la taille (TPMT/h) <16,8 mm/m. Deux groupes ont été définis (G1/G2: présence/absence de sarcopénie) et comparés par rapport à leur survie et la survenue de complications ultérieures.

Résultats : Soixante-dix patients inclus d'âge moyen de 62 ans, un sex-ratio de 0,8 avec un score MELD moyen de 12,81. Une sarcopénie était notée chez 44 patients (63%). A l'inclusion, les caractéristiques des 2 groupes étaient comparables mis à part la prédominance féminine et d'ascite réfractaire dans G1. Au terme du suivi moyen de 21 mois, la sarcopénie était associée à un nombre plus important de complications/patient (p=0,013) et à une plus longue durée moyenne d'hospitalisation/patient (p=0,001). La survie globale était diminuée dans G1 (p=0,035). Les taux de survie à 6 mois, 1 an et 2 ans étaient respectivement 42%, 30% et 24% chez G1 versus 67%, 40% et 27% pour G2. La sarcopénie était un facteur indépendant de mortalité (OR=2,5 ;95% IC[1,02-6,16]; p=0,045).

Conclusion : La sarcopénie est fréquente au cours de la cirrhose et constitue un facteur indépendant de mortalité.

Mots-clés : sarcopénie, malnutrition, cirrhose, tomodensitométrie, pronostic, mortalité

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INTRODUCTION

Sarcopenia is defined as muscle mass and function reduction. It is a common complication that reflects malnutrition in chronic diseases, such as advanced liver diseases. Nevertheless, classical nutritional assessment in cirrhotic patients, using standard tools (i.e., body mass index, albumin, transferrin, mid arm muscle circumference…), is unreliable due to the usual fluid retention, hepatic failure and interobserver variability. In the last decade, different radiological methods were used to assess nutritional status such as cross-sectional imaging, bioimpedance analysis (BIA) and dual-energy X ray absorptiometry (DEXA), showing a good performance results. These methods were first described in oncology and then were extended to other chronic diseases. Cross-sectional imaging is now considered the gold standard for nutritional evaluation and muscle mass assessment in hepatology [1–3], especially that it is routinely performed in cirrhotic patients (LT evaluation, hepatocellular carcinoma screening…).

In cirrhotic patients undergoing liver transplantation (LT), sarcopenia was found to be an independent prognostic factor associated with septic complications and longer intensive care stay after LT [4,5]. Managing sarcopenia by different nutritional approaches would be beneficial for cirrhotic patients in terms of survival after LT. However, the impact of sarcopenia in cirrhotic patients apart from LT outcomes is less investigated. This seems even more important in countries where LT is not easily available, resulting in a long period of time through which clinicians are faced with end-stage liver diseases. Therefore, our study aimed to determine the prevalence of sarcopenia in Tunisian non-transplanted cirrhotic patients and to evaluate its clinical impact on morbidity as well as mortality during follow-up.

METHODS

Study design and study population

A monocentric longitudinal retrospective study was conducted in the gastroenterology department of Charles Nicolle university hospital, Tunis, Tunisia. We included all adult cirrhotic patients, who already had abdominal computed tomography (CT) done for any indication, from 01/01/2014 to 20/03/2020. Inclusion time corresponded to the date of CT scan. We excluded patients with a follow-up less than six month, those with uninterpretable CT scans, patients aged 80 years old or over and those suffering from other diseases responsible of sarcopenia (solid cancers except hepatocellular carcinoma (HCC), untreated hyperthyroidism advanced heart or pulmonary failure, end-renal stage failure on hemodialysis, inflammatory chronic diseases, and neurodegenerative diseases). Patients were divided into 2 groups according to the CT defined sarcopenia: Group 1 (G1) with sarcopenia and group 2 (G2) without sarcopenia. Patients were retrospectively followed until 31/12/2021.

Data collection

The baseline characteristics at inclusion time (age, sex, body weight, body mass index (BMI), medical history, etiology and severity of underlying liver disease, previous cirrhosis complications) were collected. We recorded the different complications and outcomes occurring during follow-up: ascitic decompensation, icteric decompensation, hepatic encephalopathy (defined according to west haven criteria) [6], variceal bleeding, bacterial infections, hepatocellular carcinoma, acute kidney injury, portal vein thrombosis and death. We also calculated the average number and duration of hospital stays in the year following the CT.

Imaging Analysis

To determine the presence or absence of sarcopenia, we used the transversal psoas muscle thickness (TPMT) at the level of the umbilicus, according to Durand et al. method [7].

Transversal psoas muscle thickness was measured by the diameter of psoas muscle perpendicular to the axial diameter, as it is shown in Figure 1. Then, the psoas muscle thickness was normalized to the patient's height (TPMT/h). The measurement was done by a hepatologist after a first demonstration and initiation by a radiologist. Sarcopenia was defined as TPMT/h <16.8 mm/m for sex-nonspecific TPMT-sarcopenia, according to previously published cutoffs in the literature [7].

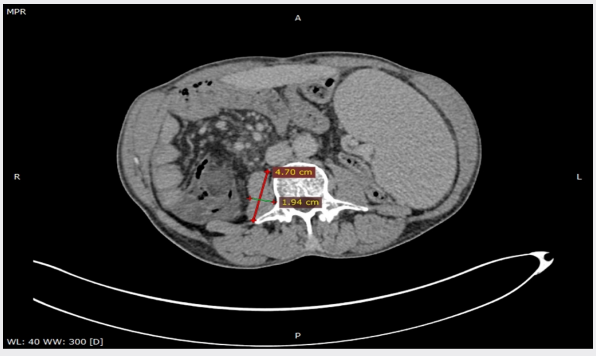

Figure1. Axial abdominal CT scan image at umbilicus level in 64 years-old patient and 1.68 m of height. The red arrow represents the axial diameter of the psoas muscle and the perpendicular green cross the transversal diameter measured in mm (19.4 mm). The TPMT/h was egal to 11.54 mm/m.

Statistical analyses were performed using the Statistical Package for the Social Science (SPSS) version 24.0. All data are expressed as either mean ± standard deviation for continuous variables or number of patients (percentage) for categorical variables. Groups were compared using the chi square test for categorical variables and Student's t-test for quantitative variables. Survival time was calculated as the time interval from the date of the abdominal CT scan to death or to the end of the follow-up. Survival curves were constructed using the Kaplan-Meier method, and differences were assessed by the log rank test. A Cox regression analysis was performed to find which variables were predictors of mortality. The multivariate cox model included the variables with p <0.2 in univariate analysis as well as gender and age. Hazard ratios (HRs) and 95% CIs were calculated. A two-tailed P-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 70 patients were included (Figure 2). The baseline characteristics of included patients are summarized in Table 1.

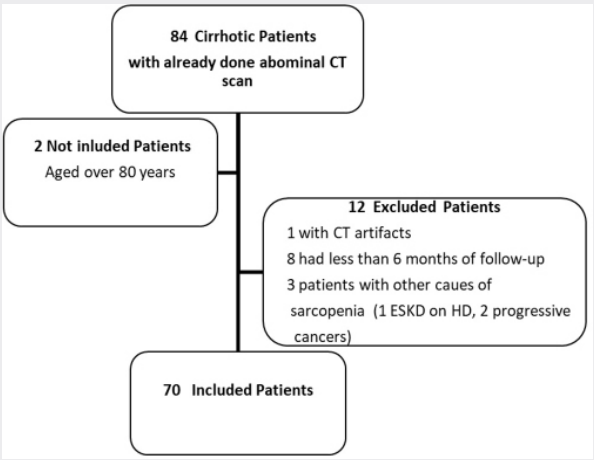

Figure 2. Study Flow diagram

CT: computed tomography; ESKD on HD: End of Stage Kidney Disease on Hemodialysis.

Chronic viral hepatitis represented the most underlying etiology (n= 41; 59%) with HVB infection and HCV infection noted in 48% and 11% of cases respectively. Average MELD score at inclusion time was 12.81 ± 4.45 [7 - 26].

The median follow up was 21 months. During the first 12 and 24 months of the study, 11% and 31 % of patients respectively were lost to follow-up

Sarcopenia frequency and main characteristics of sarcopenic versus non-sarcopenic groups

The mean TPMT/h of the pooled patients was 13.56 ± 4 mm/m [5.25-24.26]. According to the cut-off of 16.8 mm/m, 44 patients (63%) were sarcopenic. Baseline characteristics of the two groups were comparable except for women predominance (p=0.006) and refractory ascites (p=0.032) in the sarcopenic group.

The comparison between baseline characteristics of the two groups is summarized in **table 1**.

Table 1. Baseline Characteristics of included patients

	All patients (n=70)	Sarcopenic group (n=44)	Non sarcopenic group (n=26)	p-value
Age (years)	62± 12	61.81±8.19	62.55±13.21	0.879
Gender (M/F) (n)	31/39	17 / 9	14 / 30	0.006
BMI (kg/m²) (%)				
≤ 18. 5	16	19	14	0.175
18.5-25	38	50	32	
≥25	46	31	54	
Smoking (%)	19	30	17	0.209
Mellitus diabetes (%)	29	35	25	0.390
Blood Hypertension (%)	30	35	27	0.517
Alcohol consumption (%)	14	12	17	
Underlying liver disease				
Viral (%)	59	59	59	0.840
Non-viral (%)	41	41	41	
Time since cirrhosis diagnosis (months)	36±38	35,04±6,71	37,11±6,31	0.807
MELD score (%)				
<15	76	77	75	0.785
15-20	21	23	21	
>20	3	0	4	
Child Pugh (%) A	37	46	32	0.092
B	42	46	39	
C	21	8	29	
Ascites (%)	61	54	64	0.652
Refractory Ascites (%)	10	0	16	0.032
Hepatic encephalopathy (%)	7	4	9	0.644
Variceal Bleeding (%)	34	27	39	0.436
Concomitant HCC (%)	21	23	21	0.796

MELD: model for end stage liver disease; HCC: hepatocellular carcinoma

Patients Outcomes and survival

At least one complication was noted in 89% of included patients. Comparison of frequency and complication type between the two groups is represented in table 2. Sarcopenia was significantly associated with a higher number of complications per patient

(2.8 vs 1.7; p=0.013) and a longer mean hospital stay duration per patient (17.11±15 vs. 5.8 ±7days; p=0.001) during the first year of follow-up. The mean number of hospitalizations per patient and per year was higher in the sarcopenic group (1.54 vs 1.19) but with no statistical significance.

Table 2. Cirrhosis complications during follow-up

	Non sarcopenic (n=26)	Sarcopenic (n=44)	P
Hepatic encephalopathy (%)	25	27	0.859
Refractory Ascites (%)	35	45	0.390
Ascites (%)	75	69	0.600
Icteric decompensation (%)	21	27	0.692
Bacterial Infections (%)	67	31	0.634
Spontaneous bacterial ascites infection (%)	5	4	0.691
Acute Kidney injury (%)	16	15	0.618
Variceal Bleeding (%)	29	31	0.914
HCC (%)	14	37	0.039

HCC: hepatocellular carcinoma

Median overall survival was 33±4.7 months. The mortality rate was 41% (n=29) with more deaths occurring in sarcopenic patients than non-sarcopenic (21/44 vs 8/26), but with no statistical significance (p=0.164). The main causes of death in patients with sarcopenia were due to variceal hemorrhage (29%, n=6), sepsis (24%, n=5) and hepatic encephalopathy (19%, n=4). However, cumulative survival rate differed significantly according to the presence of sarcopenia with log-rank=0.035 (Figure 3). Survival rates at 6, 12, and 24 months were 67%, 40%, 27% respectively in patients without sarcopenia, versus 42%, 30% and 24% respectively in patients with sarcopenia.

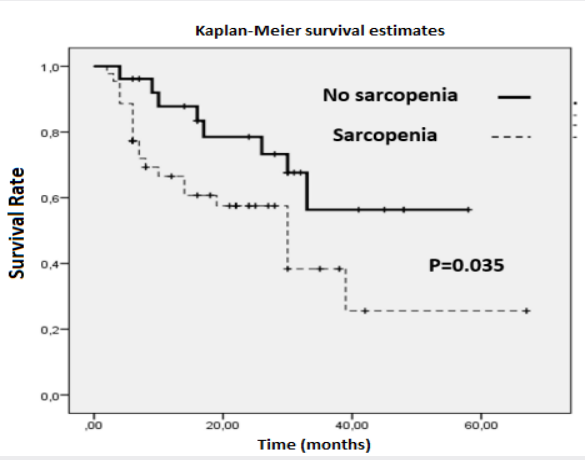

Figure 3. Kaplan–Meier curves indicating patients' survival with and without sarcopenia.

Predictors of mortality in cirrhotic patients

Univariate analysis of overall survival found five mortality-associated variables with p-value <0.2: variceal hemorrhage, hepatic encephalopathy, number of complications per patient, mean duration of hospitalization and sarcopenia. In the multi-variate cox regression, only sarcopenia and hepatic encephalopathy were independent predictors of mortality in our patients (Table 3).

Table 3. Predictors of mortality at the multi-variate cox regression

	HR (95%CI)	P
Sarcopenia	2.511 [1.022-6.166]	0.045
Hepatic Encephalopathy	3.590 [1.566-8.231]	0.003

DISCUSSION

This study is, to the best of our knowledge, the first Tunisian study evaluating the frequency of radiological sarcopenia in cirrhotic patients. We included 70 cirrhotic patients of predominantly viral etiology. Advanced liver disease (MELD >15) was noted in 24% of the cases. Radiological sarcopenia was observed in 44 patients (63%). Sarcopenia was found to be an independent predictor of mortality with an HR of 2.5 and an overall poor prognostic factor in cirrhosis. We used a radiological definition, aligning with international recommendations for the diagnosis of sarcopenia [1].

This study had, however, some limitations. Firstly, it is a retrospective and monocentric study, thus exposing to the risk of bias. The small sample size can be explained by the loss of several CT scan data. Easier access to MRI instead of CT for hepatic nodule exploration also justified the low number of included patients. In our study, we did not use MRI data to define sarcopenia as diagnostic methods still need to be validated. The survival study also had some limitations due to the loss of follow-up of some patients.

Sarcopenia frequency was 63% in our study which is consistent with published data. In fact, in cirrhotic patients, prevalence of radiologically defined sarcopenia ranged from 20% to 70%, depending on the series and methods used [8,9]. This wide difference in prevalence was partly explained by the heterogeneity of the definitions used and the baseline characteristics of the study populations as well as the spectrum of liver disease severity [8,10]. The observed high rate of sarcopenia in this study can also

be explained by the high proportion of included patients with advanced liver disease (24% of patients having Meld score > 15 and 63% having at least B score according to Child Pugh) and HCC (21%). In fact, we opted for the inclusion of patients with HCC to cover a large spectrum of disease severity as Durand et al. explained in their study.

In our population, only 16% of patients had a BMI<18.5kg/m2, consistent with the classical malnutrition definition. To our knowledge, the previously published Tunisian reports, investigating nutritional status of cirrhotic patients, used only anthropometric measures and founded conflicting results [11,12]. In fact, in a first study, published in 2010 and including 44 Tunisian cirrhotic patients, 79.5% of patients were found to be malnourished according to arm muscle circumference (AMC) [12]. Ennaifer et al. in their cohort of 104 cirrhotic patients with a comparable disease severity, founded a prevalence of malnutrition of 16% vc 32% according to BMI and AMC respectively[11]. This emphasizes more the limits of anthropometric data used to assess nutritional status in cirrhosis.

Cross-sectional imaging corresponds to the gold standard for diagnosis of sarcopenia according to several liver disease guidelines (EASL 2018, ESPEN 2020, AASLD 2021) [1,8,13]. Several radiological measurement parameters have been proposed apart from TPMT/h such as: Skeletal Muscle Index (SMI), Total Psoas Area (TPA), Psoas muscle index (PMI). The recommended radiological parameter to be used is still a subject of controversy [13]. SMI has long been the most widely used parameter. Given the relative complexity of the latter and the need for sophisticated software for measurement, we chose TPMT/h as a simple reproductible parameter that is increasingly used [7]. Importantly, clinician analysis of CT slices using TPMT/h has been found to be reliable with inter-operator reproducibility greater than 0.95 [14].

Most studies investigated sarcopenia's effects on post-LT morbidity and mortality. However, reports investigating the effects of sarcopenia on the occurrence of liver related complications in cirrhotic patients awaiting LT are scarce. Merli et al. reported , in a prospective cohort of 300 cirrhotic patients, that sarcopenia was an independent risk factor for both overt and minimal hepatic encephalopathy (OR=3.4; 95 % CI 1.4–6.9; p<0.001) [15]. Fasting venous ammonia concentrations were also higher in the sarcopenic group [15]. This association is explained by the vicious cycle between hyperammonemia and hepatic encephalopathy. In fact, muscles contribute to ammonia clearance during cirrhosis by using branched chain amino acids (BCAAs) [16,17]. This leads to an increased muscle depletion, insufficient ammonia detoxification and consequently to more hepatic encephalopathy [18]. However, in this study, we did not find a statistically significant association between muscle depletion and occurrence of hepatic encephalopathy. It should be noted that Paternostro et al., in a more recent prospective study of 109 cirrhotic patients, did not find this association as well [19]. These discordant results may be explained by the fact that the presence or absence of HE was assessed clinically and not according to ammonia levels [19]. Thus, minimal hepatic encephalopathy was not considered in the above-cited study nor in our series.

Regarding other complications, we did not find any association with sarcopenia. Nevertheless, we observed, in the sarcopenic group, a higher average number of complications per patient (p=0.013) and a longer average length of hospital stay per patient (p=0.001). We also noted an increased number of hospitalizations in patients with sarcopenia but without statistical significance. However, we only managed to evaluate hospital stays in the first year after the CT scan as 31% patients were lost to follow-up. To note, 11% of patients were lost to follow up during the first year after CT scan. More studies in literature found similar results [20,21]. Welch et al. analyzed the records of 106,835 cirrhotic patients over the period of 4 years. They founded that sarcopenia in hospitalized cirrhotic patients, in different age stratum (>65 years, ≤50 , 51–65) was significantly linked to a higher cost of hospitalization and a longer length of stay [20].

Apart from morbidity, literature have shown that the presence of radiological sarcopenia is associated with increased mortality in cirrhosis in post-LT [8,10]. The metaanalysis of Vugt et al. gathered 20 studies that only used CT parameters, concluded that sarcopenia was associated with higher mortality rates in pre-LT (OR=1,72; 95%IC [0.99–3.00];I^2=33%; p=0,02) and post-LT(OR =1,84; 95%IC [1.11–3.05]; I^2=60%; p=0.02) [22]. Paternostro et al. compared different CT methods and found that TPMT/h was the only predictive factor of mortality when comparing it to SMI for instance, without however advancing an explanatory hypothesis [19]. Our study reinforces these findings by showing that sarcopenia, defined according to the TPMT/h, as an independent predictive factor of

mortality with a HR of 2,5. Moreover, several studies advocated recently the incorporation of sarcopenia into the MELD score for better selection of cirrhotic patients for LT. Montano-Loza et al. in a study of 298 patients with cirrhosis showed that the novel score MLED-sarcopenia moderately improved the prediction of mortality in patients with low MELD scores [23].

CONCLUSION

This study emphasizes the high prevalence of sarcopenia in cirrhosis and suggests its highly negative impact on morbidity and mortality of non-transplanted cirrhotic patients. It highlights the importance of screening for sarcopenia in patients with cirrhosis. Abdominal CT scan offers an objective and available tool for clinicians for sarcopenia diagnosis. In particular, the use of TPMT/h is easy and reproducible. Nevertheless, although not included in usual cirrhosis prognostic scores, presence of sarcopenia should thus alert hepatologists, to a similar degree as other cirrhosis complications, and impose adequate nutritional management (i.e. supplementation with BCAAs) to improve patients' prognosis. Prospective, multicenter, and larger studies would be of great value to assess the true prognostic value of sarcopenia and the prognostic value of MELD-sarcopenia score.

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