

Impact of Psoas Muscle Wasting Among Cirrhotic Patients Awaiting Liver Transplantation: Predictor of Mortality and Transplant Selection

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ABSTRACT

Introduction: In this study were included patients with liver cirrhosis waiting for liver transplantation. The study aims were to assess the prevalence and predictors of decreased muscle mass which is a frequent finding in liver cirrhosis associated with a poor prognosis.

Material and Method: The study included 133 patients with liver cirrhosis, who were split into two groups, low and high, based on their psoas muscle index (PMI). The PMI was calculated using the area of the psoas muscle measured on CT or MRI images and normalized by the square of the patient's height. The sex-stratified median PMI value of 6.84 cm²/m² for men and 4.88 cm²/m² for women was used as the threshold for low or high PMI.

Results: The results showed that patients with low PMI were more likely to have, ascitic decompensation OR=6.495, p<0.001, prolonged hospitalization p=0.009 and need for intensive care OR=4.966, p=0.046 and a MELD-Na score > 21 OR=2.211, p=0.044. Significant predictors of mortality were the presence of ascites HR=4.123, p=0.010, MELD-Na score > 21 HR=2.266, p=0.046 and a history of alcohol-related liver disease HR=0.273, p=0.005. Patients with low PMI also had a higher risk of 1 year mortality, with a HR of 5.547 than the high PMI patients p=0.01.

Conclusion: In conclusion decreasing muscle mass is a frequent complication of liver cirrhosis and is associated with a poor prognosis. These results suggest that clinicians should be aware of risk factors as low muscle mass and should consider measuring PMI in cirrhotic patients waiting for liver transplantation.

Key words: liver cirrhosis, alcohol-related, low-psoas muscle index, transplantation, mortality

BACKGROUND

Malnutrition has up to 50% prevalence in the general population (1) and is a common condition in patients with severe chronic diseases. It is also a common complication in liver cirrhosis especially in decompensated stage and is considered an independent predictor for survival (2-4). Among decompensated cirrhosis, as the severity of the disease progresses, malnutrition affects up to

Received: 03.05.2024

Accepted: 20.06.2024

80% of patients (5) and almost 100% of patients awaiting liver transplantation have some degree of malnutrition (6).

There are multiple mechanisms that cause malnutrition in the decompensated stage of cirrhosis, regardless of the cause of the liver disease: anorexia and the onset of ascites, changes in the metabolic status, with acceleration of protein catabolism and compromised nutritional status (5). Malnutrition also leads to the progressive loss of muscle mass which is termed sarcopenia. The definition of sarcopenia in the geriatric literature considers decreased muscle strength and reduced muscle mass. In cirrhosis, sarcopenia specifically refers to depletion of muscle mass (4,7).

Primary sarcopenia associated with the normal aging process, in the general population, affects up to 30%, but in cirrhotic patients, secondary sarcopenia has a prevalence of 40% (8) and up to 70% in patients with decompensated liver disease (9,10).

The development of sarcopenia in liver disease increases the risk of complication onset and is an important potential predictor and associated with 2-fold higher risk of mortality (4,8,11). Some studies show that alcohol related liver disease patients had over 37.5% prevalence of sarcopenia (11) to nearly 60% in other (12), increasing the risk of mortality, consequently the assessment of malnutrition with all its components is necessary from the moment of admission (11).

Indirect methods for evaluation of sarcopenia, involves anthropometric analysis easy to perform, requiring only trained personnel and simple instrumentation. The measurements include circumference of the middle arm, the skinfold and the level of the brachial triceps, weight, height, and body mass index (BMI) calculation. Direct methods measure cross-sectional computer tomography (CT) or magnetic resonance imaging (MRI) at the level of the L3 vertebra, directly skeletal muscle mass or psoas muscle mass (13). For the cirrhotic population, the psoas muscle index is considered a simple and predictive method, not being influenced by the presence of ascites, as shown in the 2018 revised European Sarcopenia Consensus (10).

MATERIAL AND METHOD

The present observational study, prospectively included adults with liver cirrhosis, who presented consecutively in our department, between March 2015 and May 2018, to be included on waiting list for liver transplantation and all were followed up until May

2023. According to the final event, they were classified as deceased, transplanted or alive. The inclusion criteria in the study were patients with liver cirrhosis of various etiologies with or without hepatocellular carcinoma (HCC), HCC within the Milan criteria who underwent abdominal CT or MRI at the first admission to our department.

Our first objective was to identify the prevalence and predictors of muscle loss among cirrhotic population awaiting liver transplantation. The second aim was to correlate the independent prognostic factors with survival and mortality risks and search for possible new selection factor for liver transplantation. (14). Were included in this study 133 patients with cirrhosis who underwent a CT or MRI scan with a cross-section through the L3 vertebra and the psoas muscle. Patients with alcoholic hepatitis, acute liver failure, HCC extra Milan and those relisted were excluded.

The psoas muscle is a deep muscle that seems not to be directly affected by abdominal distension in patients with ascites (15,16), this being the recommendation for the assessment of sarcopenia (10). The two diameters of the left and right psoas muscles were measured on CT or MRI images and the calculated area approximated with an elliptical shape (17,18). The average of the areas was normalized by the square of the patient's height.

Anthropometric data middle 1/3 arm circumference (MAC), triceps brachial skinfold (TSF), weight and height, chest and waist were not used in this study. Skinfolts, are mainly used for estimation of the subcutaneous fat, and arm circumferences are affected by peripheral edema, physical training, the muscles differences due to bilateral asymmetry and less by ascites presence (19). Waistline is strongly influenced by the large volume of ascites. These are considered the easiest procedures to assess nutritional status, but are vulnerable to inter-observer variability and subject hydration status (13,19). BMI was calculated for the whole group of patients, but some of them were misclassified due to the presence of ascites, therefore BMI was corrected with the estimated ascites volume, to obtain dry BMI, which was subsequently the only one used in the study.

Next, for the cirrhotic population, we choose to use the median PMI stratified by sex, the threshold for men $6.84 \text{ cm}^2/\text{m}^2$ and for women $4.88 \text{ cm}^2/\text{m}^2$ (20) and defined patients as having low PMI below these values (18). Since there is still no standardized limit for sarcopenia in the Romanian population, we chose to use the low and high PMI classification (18,21,22).

Statistical analyses

All data were analyzed using SPSS 20.0 for Windows. Continuous variables were reported as median and interquartile range or mean and standard deviation according to their distribution. Categorical variables were reported as frequencies and percentages. For continuous variables comparison were evaluated with Independent-Samples T Test or np Independent Samples Mann-Whitney U Test and Pearson Chi-Square or Fischer’s Exact Test when appropriate. Significant independent predictors for low-PMI in univariate analysis were included in multivariate analysis using binary regression. Survival estimation was performed with the Cox proportional hazard model for the study of mortality and transplantation endpoints. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Among the 133 patients, men were 76.7% with a median age of 53 years, cirrhosis related to alcohol

consumption (only or combined with other etiology) was the most common 73.7%, and non-alcoholic etiology only 26.3%. Active drinkers at the enrollment were 45.1 %. Ascites was present in 63.9% of patients from mild to large volume. HCC was present in 28.6%, median number of nodules was 2 with a diameter of 27 mm. Overall mean BMI was 23.9 kg/m². Model of End-stage Liver Disease (MELD) score had a median of 15 points and MELD-Na score 17. Length of hospitalization has a median time of 7 days and 11 (8.3%) patients were admitted in Intensive Care Unit (ICU) during first hospitalization.

The median PMI value sex-stratified divided the patients into relatively equal groups with low PMI and high PMI, and the analysis of the differences between the groups was illustrated in *table 1*. Low PMI was found in 67 patients (50.4%), of whom 51 were men, with a mean age of 52 (47-61) years. Alcohol-related liver cirrhosis (ARLC) was associated in 80.6% with reduced PMI and patients with non-alcoholic cirrhosis had higher PMI, $p = 0.068$. Half of the patients with reduced muscle mass reported active alcohol

Table 1 - Baseline characteristics of the patients at the time of listing according to the presence of low PMI vs high PMI

Characteristics	Psoas muscle index			p value
	Overall n = 133	Low PMI n = 67 (50.4)	High PMI n = 66 (49.6)	
Males (%)	102 (76.7)	51 (50)	51 (50)	0.875
Age (years, IQR)	53 (47-61)	52 (47-61)	55 (47-60)	0.978
Cirrhosis Etiology (%)				0.068
ARLC	98 (73.7)	54 (80.6)	44 (66.7)	
Other	35 (26.3)	13 (19.4)	22 (33.3)	
Active drinkers (%)	60 (45.1)	34 (50.7)	26 (39.4)	0.230
Recent abstinence (0-6 mo) (%)	47 (35.3)	19 (28.4)	28 (42.4)	
Long abstinence/Nondrinkers (>6 mo) (%)	26 (19.5)	14 (20.9)	12 (18.2)	
Ascites (%)				< 0.001
No	48 (36.1)	11 (16.4)	37 (56.1)	
Mild	22 (16.5)	14 (20.9)	8 (12.1)	
Moderate	22 (16.5)	16 (23.9)	6 (9.1)	
Large/Refractory	41 (30.8)	26 (38.8)	15 (22.7)	
HCC (%)	38 (28.6)	21 (31.3)	17 (25.8)	0.476
HCC (nodule no., IQR)	2 (1-3)	1 (1-3)	2 (1-3)	0.848
HCC dimension (mm, IQR)	27 (18-39.25)	27 (18-42)	26 (19-36)	0.531
BMI (kg/m ² , mean, S.D.)	25.16 ± 5.30	23.11 ± 4.54	27.23 ± 5.22	< 0.001
Underweight	10 (7.5)	7 (10.4)	3 (4.5)	< 0.001
Normal	53 (45.1)	45 (67.2)	15 (22.7)	
Overweight/Obesity	48 (47.4)	15 (22.4)	33 (72.7)	
Hospital stay (days, IQR)	7 (4-12)	9 (5-19)	5 (3-9)	0.001
ICU admission (%)	11 (8.3)	9 (81.1)	2 (18.2)	0.055
MELD (points, IQR)	15 (11-20)	15 (11-21)	15 (10-19)	0.340
MELD-Na (points, IQR)	17 (11-22)	19 (12-24)	17 (10-20.5)	0.045

ARLC: Alcohol Related Liver Cirrhosis; BMI: body mass index; HCC: hepatocellular carcinoma; MELD/ MELD-Na: Model for End-stage Liver Disease/Sodium; ICU: Intensive Care Unit; IQR: Interquartile Range; PMI: psoas muscle index

consumption $p=0.230$. These patients had a 4-day longer hospital stay ($p=0.001$) than patients with high PMI and 81.1% of those who required intensive care were sarcopenic $p=0.055$. Dry BMI as a continuous variable showed significant differences between groups $p<0.001$, and the highest incidence of low muscle mass was found in the normal BMI group 67.2% with $p<0.001$, when we evaluated BMI as a categorical variable. Ascitic decompensation was also significantly associated with low muscle mass $p<0.001$ especially in moderate and large volume. The presence of HCC, the number or size of nodules, had no statistical significance. Of the MELD and MELD-Na severity scores, only the latter showed a significant difference between groups with a median of 19 in those with low PMI $p=0.045$.

Predictive factors for decreased muscle mass in liver cirrhosis and the probability that they determine low PMI were evaluated in univariate analysis. We included one potential predictor for every 15 patients (table 2).

Univariate analysis reveals that cirrhosis etiology was not significant associated with muscle wasting (OR 2.08, 95% CI 0.94-4.58, $p=0.071$) and the chance of low PMI in ARLC was 2-fold lower than other etiologies. This model rise the prediction accuracy to 57.1%. The HCC presence was 1.3 more likely to be associated with low PMI (OR 1.32, 95% CI 0.62-2.80, $p=0.476$). Although overall mortality did not significantly differ between the two groups, the odds of reducing muscle mass was 4.6% per month (OR 0.93, 95% CI 0.86-1.01, $p=0.089$) improving the prediction by 10%. A MELD-Na score >21 points was associated with more than 2.2 times higher chance that the patient will present low PMI (OR 2.211, 95% CI 1.023-4.776, $p=0.044$). BMI and PMI showed a negative correlation, BMI being a very good predictor with a model accuracy of 75.2%, OR 0.822, 95% CI

0.749-0.903, $p<0.001$. Ascitic decompensation increases the probability of being low PMI by 6.5 times (OR 6.5, 95% CI 2.89-14.58, $p<0.001$). Prolonged hospitalization is positively correlated, with a 2-fold higher chance of a decrease in PMI (OR 1.06, 95% CI 1.01-1.10, $p=0.009$), and ICU admission increases the odds to 5-fold (OR 4.97, 95% CI 1.03-23.94, $p=0.046$) for low PMI. With the increase of survival on the waiting list, the chance of reducing muscle mass was lower by 4.6% every month, the difference was not significant $p=0.070$. In the multivariate analysis, we entered the significant predictors from the univariate analysis and the result was that ascites (OR 4.25, 95% CI 1.79-10.07, $p=0.001$) and BMI (OR 0.87, 95% CI 0.79-0.95, $p=0.003$) are independent predictive factors for the decrease in muscle mass.

During the study period (72 months), 26 (19.5%) of the subjects died, 31 (23.3%) were transplanted and 76 (57.1%) are still waiting.

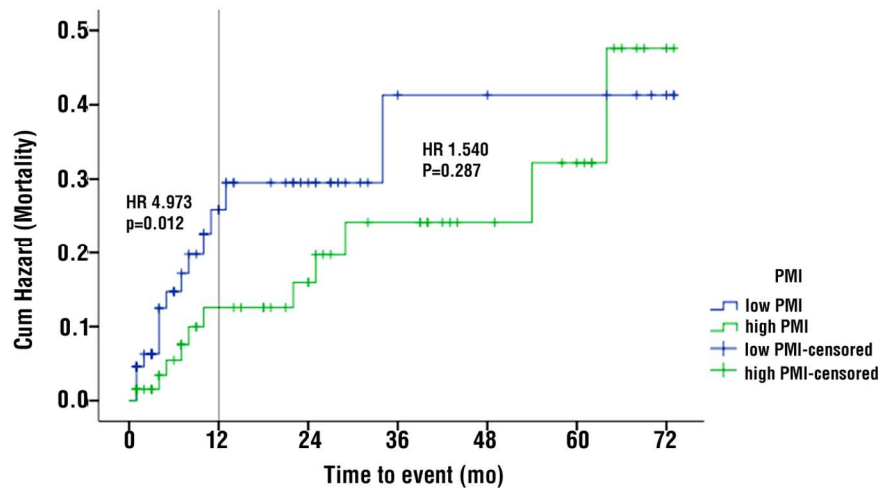
The 6-year survival in patients without HCC was 1.68 times higher compared to those with HCC, the difference not being significant $p=0.215$. Alcohol-related cirrhotic patients had a 46.3% longer survival chance compared to other causes $p=0.137$. PMI value does not significantly influence long-term survival, low PMI patients having 1.54 times higher mortality than the rest $p=0.287$ (fig. 1). A MELD score >17 increases the odds of death by 2-fold, $p=0.074$ close to significance compared to those with lower MELD. MELD-Na score >21 was significantly different in predicting long-term mortality by 2.27 higher odds for those with low PMI $p=0.046$. Patients with ascitic decompensation had an estimated survival time 4.123 times shorter than patients without ascites, $p=0.010$, and the odds of survival decrease 4.3 times in patients requiring intensive care $p=0.009$.

Table 2 - Univariate and Multivariate binary regression analyses for predictors of low PMI

Predictor	Univariate analysis			Multivariate analysis		
	OR	95% CI	Sig.	OR	95% CI	Sig.
ARLC	2.077	0.940-4.589	0.071			
HCC	1.316	0.618-2.801	0.476			
MELD > 17	1.472	0.711-3.047	0.297			
MELD-Na > 21	2.211	1.023-4.776	0.044			
BMI	0.882	0.749-0.903	<0.001	0.866	0.788-0.952	0.003
Ascites	6.495	2.893-14.583	<0.001	4.250	1.793-10.073	0.001
Hospital Stay	1.058	1.014-1.104	0.009			
ICU	4.966	1.030-23.935	0.046			
Time to death	0.954	0.906-1.004	0.070			

ARLC: Alcohol Related Liver Cirrhosis; HCC: hepatocellular carcinoma; MELD/MELD-Na: Model for End-stage Liver Disease/Sodium; BMI: body mass index; ICU: Intensive Care Unit; PMI: psoas muscle index; OR: Odds Ratio; CI: confidence interval; Sig.: significance

Figure 1 - Mortality according to PMI. The significance at 1 year and 6 years follow-up



In the multivariate analysis of long-term waiting list mortality, we found significant predictors: the presence of ascites $p=0.002$, non-alcoholic etiology $p=0.010$ and the need for intensive therapy $p=0.014$. (table 3).

For 1-year mortality rate, PMI was an excellent predictor with 4.973-fold HR of death in the low PMI group (95% CI 1.429-17.311, $p=0.012$) (fig. 1), as expected, MELD-Na was a significant predictor HR 2.928 (95% CI 1.129-7.593, $p=0.027$). Ascites and ICU admission were also significant predictors $p=0.026$ and $p=0.001$. In the multivariate analysis we found the same independent predictor variables as those found for long-term mortality; non-ARLC predictor for first year transplantation $p=0.011$, ascites $p=0.015$ and ICU admission $p < 0.001$.

For liver transplantation as an end point, the presence of HCC (12-months $p = 0.594$ and 50-months $p=0.577$), alcoholic or non-alcoholic etiology patients ($p=0.848$ vs. $p=0.977$) were equally transplanted.

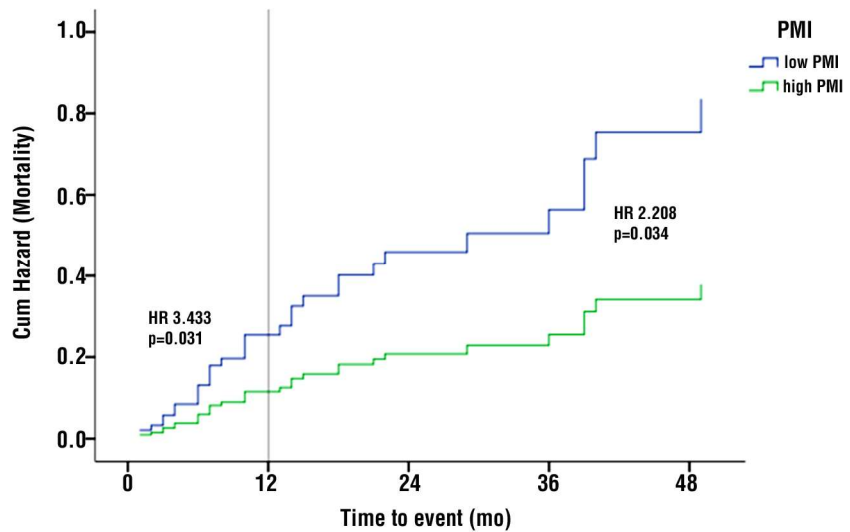
Regarding alcohol consumption, significantly fewer active users were transplanted over the 72 months compared to non-drinkers (as a reference group) $p=0.041$ and no significant difference between the transplanted long-abstinent (> 6 months) patients and the same baseline group $p=0.282$, and at 12 months no significant differences were found ($p=0.114$ and $p=0.160$). Ascitic decompensation prioritized 2 times more cirrhotic patients for transplantation during the 6 years of study and only 1.368 in the first year. Each additional point in the MELD score increased the chance of being transplanted but not significant at 12 or 50 months. MELD-Na score with HR 1.056, 95% CI 1.005-1.110, $p = 0.032$ was significant only for long term selection. Muscle mass decrease, increases the chance of low PMI patients to be transplanted for 3.433 times $p = 0.031$ in the first year and for 2.208 times $p=0.034$ in long term follow-up (fig. 2).

Table 3 - Univariate and Multivariate Cox Regression analyses for predictors of 6 years (long-time) mortality on the waiting list

Predictor	Univariate analysis			Multivariate analysis		
	HR	95% CI	Sig.	HR	95% CI	Sig.
HCC	1.679	0.740-3.814	0.215			
ARLC	0.573	0.237-1.219	0.137	0.273	0.111-0.671	0.005
LOW PMI	1.540	0.695-3.412	0.287			
MELD >17	2.061	0.933-4.555	0.074			
MELD-Na >21	2.266	1.013-5.069	0.046			
Ascites	4.123	1.399-12.153	0.010	5.712	1.780-18.333	0.003
ICU admission	4.290	1.436-12.815	0.009	4.135	1.331-12.841	0.014

HCC: hepatocellular carcinoma; ARLC: Alcohol Related Liver Cirrhosis; LOW PMI: low psoas muscle index; MELD/MELD-Na: Model for End-stage Liver Disease /Sodium; BMI: body mass index; ICU: Intensive Care Unit; HR: Hazard Ratio; CI: confidence interval; Sig.: significance

Figure 2 - Liver transplantation according to PMI. The 12 months and 50 months follow-up



DISCUSSIONS

In the last 2 decades, malnutrition and sarcopenia have become an important topic of study in the cirrhotic patient being more prevalent in men (23). Extrapolating the definition of malnutrition and sarcopenia from the elderly population, developed by the EWGSOP in 2010 and revised in 2019 to the cirrhotic population, the most accurate muscle parameter for the cirrhotic patient, reproducible assessment method, standardized and adjusted for different ethnicities, sex-stratified cut-off to define sarcopenia is still sought. Currently, several methods are available to assess muscle mass and estimate sarcopenia in cirrhotic patients, but no consensus has been reached yet. Most studies quantify sarcopenia using skeletal muscle mass and SMI with more specified cutoff values (24), but others use psoas muscle mass and PMI parameters. In a study from Turkey, cut-off values are established for both parameters to be used in clinical practice (25). The recommendation of the EWGSOP (European Working Group on Sarcopenia in Older People) is to use norms from healthy young adults to define the cut-off values (12, 14). Also, the standardized values must be adjusted according to the characteristics of the population (26). Studies reporting cut-off values for sarcopenia in healthy liver donor populations had values with wide variations by ethnicity, PMI in men between 4.24 - 7.8 cm^2/m^2 and 2.5 - 6.4 cm^2/m^2 for women (11; 25; 27-30). For the population in our country there is still no consensus for sarcopenia, so in our study on the cirrhotic population, we considered it appropriate to use the parameters of the psoas muscle with the

median PMI values stratified by sex, which are independent of fluid retention (31) and we defined subjects as low PMI $\leq 6.84 \text{ cm}^2/\text{m}^2$ for men and $\leq 4.88 \text{ cm}^2/\text{m}^2$ for women or high PMI groups above these values.

The clinical significance of decreased muscle mass (sarcopenia) and its consequences in the course of liver disease have increased; some data support the idea that it has an impact on the frequency of decompensation, increasing length of hospital stay and mortality, and offers the possibility of better prioritizing patients on the waiting list (32).

The demographic data in our study overlapped with those from most studies. Men predominated in our cirrhotic group, with a median age of 53 years, the most frequent etiology was alcohol-related and almost half were active alcohol consumers at the time of the first presentation.

The prevalence of decrease muscle mass was not significantly correlated with increasing age or with alcohol-related etiology of liver disease. In contrast to other studies where ARLC was strongly associated with malnutrition and low muscle mass, especially in those with active alcohol consumption (33). The HCC presence, the number of nodules or the size were not significantly associated with the reduce muscle mass, in contrast with many other studies describing a high prevalence of sarcopenia among patients with HCC. An explanation could be that our cohort consisted of patients only within the Milan criteria and consequently the tumor load was limited (34).

BMI was significantly positively correlated with PMI and divided by groups, it showed that in the range of normal BMI patients with low PMI predominated, so

sarcopenia should be evaluated in both underweight and normal weight patients. Some authors find the same results, that malnutrition was most frequent among normal weight or underweight patients (14). In other studies is shown that even in the overweight or obese group there is a need for an assessment of the muscle mass, they often had occult, severe muscle depletion (35), replaced by fat mass, named sarcopenic obesity.

The severity of liver disease with a MELD-Na score of >21 points and the presence of ascites were independently associated with the risk of reduced muscle mass and the development of sarcopenia, as the prolongation of hospitalization or admission to the ICU are predictors for the reduction of muscle mass.

The connection between sarcopenia and the likelihood of survival indicates that sarcopenic patients have more than 2-fold higher risk of mortality (36), in our study the risk for low PMI was lower, just 1.5 more patients died.

Univariate Cox analysis associated mortality with ascites, MELD-Na above 21 pts. and ICU admission. By multivariate Cox analysis nonalcoholic etiology, ascites and ICU stay were independently associated with mortality. In 2014 Durand's study showed that muscle atrophy in patients with refractory ascites could be a good predictor for mortality in patients with cirrhosis (15). Our study demonstrates a low level of correlation between low PMI and long-term mortality on the wait list, but sarcopenia or low muscle mass may have a greater impact on short-term outcomes, one-year mortality is 4.97 times higher in these patients (36). Contradictory results in studies revealed, psoas muscle which is not affected by abdominal distention in cases of ascites and has been shown to be predictive of mortality in cirrhosis (37) or stated that PMI was not a predictor of waitlist mortality in cirrhotic patients (38). Although sarcopenia is not a selection criterion for LT, giving some priority to these patients with sarcopenia may help decrease mortality in patients with cirrhosis (16) at least in the first year.

Significant parameters in our study for selection of patients for transplant were MELD-Na score and PMI and time to TH, significantly decreased with decreasing PMI $p < 0.001$ and increasing MELD-Na score $p = 0.003$.

Another criterion was the period of abstinence, with non-drinkers being transplanted in relatively equal proportion to those abstinent for more than 6 months and significantly more frequently than active drinkers.

The present study brings to attention some results that could be important benchmarks in the evaluation

of patients for transplantation. The CT or MRI examination performed as part of the pre-transplant assessment should routinely include the diameters of the psoas muscles at the L3 level. A normal or increased body mass index does not exclude the presence of sarcopenia.

The association with MELD-Na score of some clinical parameters such as ascites and psoas muscle index for the prediction of mortality at 1 year on the waiting list and in the selection of patients as liver recipients, the rule of 6 months of abstinence (10), the MELD-Na score and the PMI are confirmed.

Limitations

The limitation of this study is that only the muscle mass was evaluated, not the muscle function as established in the European consensus on the definition and diagnosis in cirrhotic patients. We also consider that the best muscle mass evaluation parameter for cirrhotics is the PMI, although it is not standardized. Predefined values for sarcopenia which could be used for patients with cirrhosis are still lacking. Anthropometric measurements, mean MAC and TSF had significant differences, chest and waist circumferences were quite similar in both cohorts, but as shown previously, these measurements are affected by bias and random errors and are not recommended for routine use (13).

CONCLUSIONS

Sarcopenia assessed using PMI values measured at the third lumbar vertebra had a significant and independent impact on the selection of patients for organ allocation may provide a net benefit. The decrease in muscle mass can be associated with any BMI group. A more precise assessment of survival on the waiting list at 1 year could include, in addition to the MELD-Na score, ascitic decompensation and the assessment of muscle mass by PMI. Therefore, we should attach importance to the screening of sarcopenia in patients with cirrhosis.

Conflict of interest

All authors declare no conflict of interest.

Funding

No funding.

Ethical statement

The study protocol conforms to the 1975 Declaration of Helsinki and was authorised by the Fundeni Clinical Institute Review Board.

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