Evaluation of nutritional indicators and body composition in patients with advanced liver disease enrolled for liver transplantation[1]

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ABSTRACT

PURPOSE: Malnutrition is prevalent in patients with advanced liver disease (LD) related to multifactorial causes. Fluid retention can underestimate the nutritional status based on anthropometric measures. We evaluated nutritional indicators and body composition (BC) in patients with liver cirrhosis and correlated them with LD severity.

METHODS: Forty three patients with LD enrolled for liver transplantation were evaluated by Anthropometric measures, subjective evaluation (Global Assessment of Nutritional Status – SGA) and biochemical indicators. Single-frequency electrical bioimpedance (SFE-BIA) was used to evaluate body composition (BC). It measured resistance (R), reactance (Xc) and the phase angle (PA). LD severity was estimated by Child-Pugh and Meld criteria (Model for End-Stage Liver Disease).

RESULTS: Child-Pugh index between patients was 7.11±1.70 and Meld was 12.23±4.22. Arm Circumference, Arm Muscle Circumference and Arm Muscle Area, SGA, hemoglobin, hematocrit and albumin showed better correlation with disease severity. Xc and PA showed correlation both with Meld and Child-Pugh score when BC were evaluated. PA was depleted in 55.8% of the patients.

CONCLUSIONS: Diagnosis of malnutrition varied according to the method. Global assessment of nutritional status showed better correlation with disease severity than with objective methods. Single-frequency electrical bioimpedance for body composition analysis in cirrhotic patients must be cautiously used; however, primary vectors seems to be valid and promising in clinical practice.

Key words: Liver Cirrhosis. Nutrition Assessment. Protein Malnutrition. Electric Impedance.

Introduction

Hepatic cirrhosis (HC) is characterized by chronic and irreversible change in liver parenchyma, leading to alterations in both liver structure and in the functional capacity of hepatocytes. Together, these changes result in progressive liver function loss, thus affecting nutritional status and body homeostasis in patients with HC to a varying degrees.

Protein caloric malnutrition (PCM) is highly prevalent in patients with terminal liver disease[1]. Roongpisunthinpong *et al*.[2] suggest that PCM prevalence in chronic hepatic disease is between 10% and 100%, it is dependent on its severity regardless of disease cause. However, Malnutrition is associated with high morbidity and mortality, influencing the short and long term patient survival.

Impairment of cellular and humoral immune response in patients with HC may contribute to increased risk for infections[3], decreased quality of life and survival, increased length of hospitalizations and, therefore, increased hospital costs[4].

The subjective global assessment proposed by Detsky *et al*.[5] has been considered a good approach for subjective assessment of patients with liver disease[6], but water retention complicates its applicability since the estimated weight loss, which is part of this assessment, becomes impaired[7].

In recent studies[8-10], electrical bioimpedance (BIA) and its vectors in particular has been proposed for body composition analysis of patients with chronic liver disease[11].

Electrical bioimpedance consists in the delivery of a low-intensity (below human perceptibility) electric current[12] which flows through the body by the ions movements[13]. The opposition offered by the body to the passage of an electric current is called electrical impedance[14,15], and it is inversely related to electrical conductivity.

Given the high prevalence of malnutrition and its relationship with morbidity and mortality in patients with liver cirrhosis as well as the absence of a gold-standard method for nutritional evaluation of these patients, we conducted the present study with the purpose to evaluate prospectively the nutritional indicators and body composition in patients with liver cirrhosis enrolled for liver transplantation and correlate them with disease severity.

Methods

Forty-three patients with liver cirrhosis of different etiologies treated in nutrition outpatient units were evaluated between March 2008 and March 2009, after approval by the Ethics Committee of the Sao Paulo State University (UNESP).

Demographic included 13 (30.2%) females and 30 (69.8%) males patients, aged between 30 to 70 years and from different ethnic groups.

All patients that were included in the liver transplant waiting list presented major complications related to liver disease, with higher Meld and Child score at the time of inclusion.

Patients under the age of 18 years or undergoing treatment for hepatitis C or with a history of alcohol intake in a period less than six months were not included.

It was a cross-sectional analytical investigation, and the patients participated in interviews for clinical nutritional assessment (anthropometric, subjective and biochemical) and body composition evaluation.

A) Clinical evaluation

Disease severity was classified according to the criteria proposed by Child-Pugh *et al*.[16] and MELD - the Model for End-stage Liver Disease[17]. Due to the variation of the score of Child and Meld while on transplant waiting list, the values reported herein represent the values obtained in one given moment at the nutritional evaluation.

B) Nutritional evaluation

All subjects underwent anthropometric measurements of current weight (CW), height (H), arm circumference (AC) and triciptal skinfold (TSF). Body Mass Index for cirrhotic patients (BMI) as proposed by Campillo *et al*.[18], arm muscle circumference (AMC) and corrected arm muscle area (cAMA) were estimated.

AC, TSF and AMC classification was performed by using the percentage of adequacy through the method proposed by Blackburn and Harvey[19], and patients with percentage of adequacy <90% were considered to be malnourished/depleted. cAMA was also evaluated by the method proposed by Blackburn and Harvey[19]; however, those showing values below the 15th percentile were classified as malnourished /depleted.

The subjective global nutritional assessment was performed by the method proposed by Detsky *et al.*[5], which subjectively classifies individuals as well-nourished (A), moderately malnourished or suspected malnourished (B) or severely malnourished (C).

Biochemical evaluation included hemoglobin, hematocrit, total lymphocyte count and serum albumin. Hemoglobin and hematocrit were compared with reference values for males (14-18 g/dl and 40-57%, respectively) and females (12-16 g/dl and 37-47%, respectively).

Total lymphocyte count was interpreted according to Blackburn *et al*.[20], and values lower than 2000/mm^3 were classified as depletion. The cutoff value for albumin was <3.5 g/dl for depletion diagnosis.

C) Body composition analysis

It was performed by single-frequency electrical bioimpedance (BIA), Biodynamics model 450 (TBW), by applying an 800µA current with a frequency of 50 KHz. The following primary measurements were used: resistance (R), reactance (Xc) and phase angle. Both R and Xc were normalized by height, leading to resistance/height (R/H) and reactance/height (Xc/H), expressed as Ω/m units. Normalization is necessary considering that the absolute values vary with body size. Height is considered a good normalization index as it is not affected by fluid retention or malnutrition. They were evaluated according to their absolute values and the phase angle.

Additionally, a comparison was made according to tables of stratified values based on age and gender, as proposed by Barbosa-Silva *et al*.[14]. The values were considered to be reduced when the results were lower than the mean minus two standard deviations.

Statistical analysis

The nutritional indicators were dichotomized into malnutrition and without malnutrition or with depletion and without depletion. For analysis of qualitative variables, the Chi-square test and Fisher's exact test when appropriate ($p<0.05$), were utilized. Student's t test was used for quantitative variables for normal data.

For association of liver disease severity, nutritional indicators and bioimpedance vectors, Pearson's correlation was used. The association between disease severity and SGA and the association between bioimpedance and ascites were analyzed by multivariate logistic regression. Statistical significance was considered when $p<0.05$.

Results

Alcoholic liver cirrhosis was more prevalent (32.6%), followed by the hepatitis C virus infection (25.6%). Alcoholic liver cirrhosis alone and mixed etiology (alcohol + virus C) was observed in 48.9% of the patients.

The severity of liver disease evaluated by the Meld score varied between 12.23±4.22 and classified as Child-Pugh B (7.11±1.70). The presence of ascites was clinically determined in 65.1% of the patients at the moment of nutritional evaluation, and were under diuretics treatment.

Malnutrition diagnosis ranged from 18.6% and 79.1% by the BMI and AMA respectively as anthropometric measurements. When stratified by gender, malnutrition level varied from 23.1% (BMI and AMC) to 84.6% (AC) in females, and from 16.7% (BMI and TSF) to 83.3% (AMA) in males. AMC was the unique nutritional indicator with statistically significant difference between genders, which was more depleted in males (p = 0.007) and presented the higher MELD score (p=0.04).

Nutritional indicators showed negative correlations for both Child-Pugh method and Meld, but with higher correlations for the former. Among the indicators, AC (r= -0.38, p=0.01), AMC (r= -0.32, p=0.031) and AMA (r= -0.33, p=0.027) showed a significant correlation for the severity criteria evaluated by Child-Pugh (Table 1), suggesting that the lower the values for nutritional indicators, worse is the severity of liver disease.

TABLE 1 - Pearson's correlation between nutritional indicators and liver disease severity.

		BMI (kg/m2)	AC (cm)	TSF (mm)	AMC (cm)	AMA (cm2)
MELD	r	-0.10393	-0.166	-0.18248	-0.07042	-0.14836
	p value	0.5072	0.2860	0.2415	0.6536	0.3424
CHILD	r	-0.24387	-0.38722	-0.28618	-0.32785	-0.33717
	p value	0.1150	0.0103*	0.0628	0.0319*	0.0270*

r: correlation coefficient; BMI: Body Mass Index; AC: Arm Circumference; TSF: Triciptal Skinfold; AMC: Arm Muscle Circumference; AMA: Arm Muscle Area; * p<0.05

According to SGA, 20 (46.5%) patients presented a certain degree of malnutrition. The correlation of malnutrition odds ratio, as diagnosed by SGA, with the disease severity according to Child-Pugh, malnutrition risk increased 2.93fold for each Child-Pugh increase point (p=0.0013). However, when Meld criteria was used, no statistically significant correlation (p=0.533) was observed between liver disease severity and malnutrition by SGA (Table 2).

TABLE 2 – Fitting of the logistic regression model for SGA and disease severity indicators.

SGA	Indicator Estimate	Standard Deviation	p-value	Odds Ratio	95% Confidence Interval
Meld	-0.0716	0.1148	0.5330	0.931	0.743-1.166
Child	1.0741	0.3340	0.0013	2.93	1.521-5.633

SGA: Global Assessment of Nutritional Status; p<0.05

Total lymphocyte count (TLC) was depleted in 32 (74.4%) patients, with a weak correlation with disease severity for both Child (r= 0.17, p=0.278) and Meld (r=-0.23, p=0.146) criteria. Hemoglobin (12.93±2.4 mg/dl) and hematocrit (37.95±5.94%) values showed a negative correlation with both Meld and Child-Pugh (p<0.001).

Albumin was depleted in 21 (48.8%) patients, with a moderate negative correlation with disease severity, which was statistically significant for both Child-Pugh (r=-0.63, p <0.0001) and Meld (r=-0.43, p = 0.004). The correlation was expected for Child-Pugh criteria, considering that albumin is one of the parameters in this classification system.

The analyses of body composition demonstrated a reduced phase angle in 55.8% of the patients, according to gender and age.

The correlation of BIA parameters with liver disease severity is shown in Table 3 and illustrated in Figures 1 and 2.

TABLE 3 - Pearson's Correlation Coefficients for Bioimpedance and disease severity indicators.

Severity Criteria		R/H (Ω)	Xc/H (Ω)	Phase Angle (o)
MELD	r	-0.035175	-0.59140	-0.30947
	p value	0.0207	<0.0001	0.0434
CHILD	r	0.0429	-0.44999	-0.54219
	p value	0.7848	0.0025	0.0002

R/H: resistance/height; Xc/H: reactance/height; PA: phase angle;
Ω: ohms; *o: degrees;* BCM: body cell mass
Pearson's Correlation: p<0.05

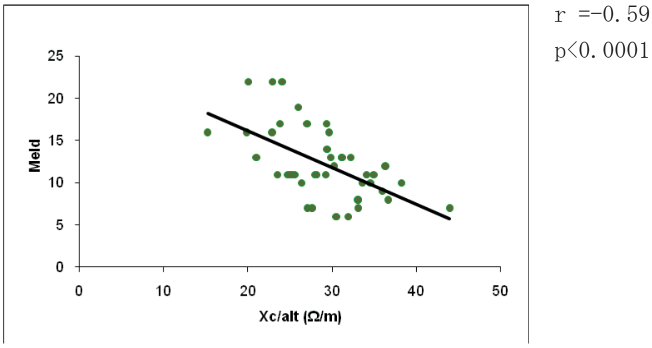

FIGURE 1 - Pearson's correlation between Meld and Xc/H.
r: correlation coefficient; Xc/ H: reactance/height

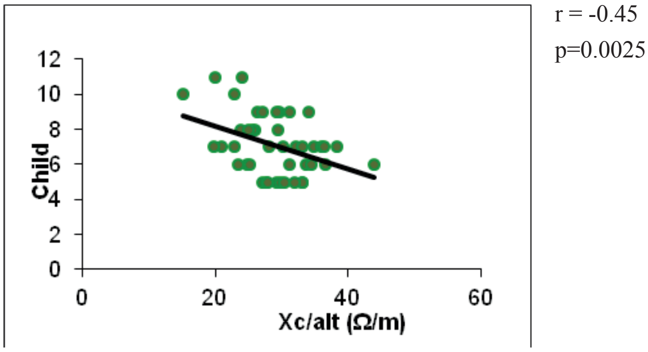

FIGURE 2 – Pearson's correlation between Child and Xc/H.
r: correlation coefficient; Xc/H = reactance/height p<0.05

According to Meld classification, there was a significant correlation for the following indicators: R (r= -0.035, p=0.020), Xc (r= -0.59, p<0.0001) and PA (r= -0.30, p=0.043), while for Child-Pugh criteria, there was significant correlation with Xc (r= -0.44, p=0.002) and PA (r= -0.54, p=0.0002). These data suggest that in increasing the severity of liver disease, lower are the values of BIA and PA vectors.

Discussion

Malnutrition should be considered one of the most important prognostic factors in HC, and alert health professionals in the same extent as the presence of other common complications such as hepatic encephalopathy and ascites[21].

For many years, malnutrition has been related to worse clinical outcomes and higher incidence of complications such as ascites, hepatic encephalopathy and infections[22], hepatorenal syndrome and diabetes mellitus. It is considered a risk factor for morbidity and mortality in short and long term before and after transplantation[23,25] as well as in abdominal surgery[21]. A recent study by Sam and Nguyen[23] showed the association of PCM with longer hospitalization (8.7 days versus 5.7 days, p<0.0001), higher in-hospital mortality and a higher rate of readmissions.

As reported in other study[10] malnutrition was also under diagnosed when Body Mass Index (BMI) was used, regardless of gender. However, malnutrition was more severe when AC and AMA were measured for females and males respectively.

One reason for the possible under diagnosed of malnutrition by BMI is related to the fluid and electrolyte retention in those patients, that may overestimate their measured weight[2]. Even though the cutoff point used was specific for cirrhotic patient, as proposed by Campillo *et al*.[18], malnutrition rates were far below those pointed out by other indicators.

Several studies have found changes in anthropometric indicators within the worsening of liver disease[1-2,8]. Alberino *et al.*[1] also refer a negative correlation between AMA and the Child-Pugh criteria, but not with TSF.

In this study, nutritional indicators showed higher correlation with the Child-Pugh criteria than with Meld. It is noteworthy that, in the previous version of the Child-Pugh criteria, malnutrition level was considered as an indicator; however, the absence of an accurate tool for nutritional diagnosis has led to its exclusion. On the other hand, Meld estimation, so far, does not take nutritional status into account. Possibly, according to Stickel *et al.*[24], this model fails in predicting survival in 15-20% of recipients of liver transplants for not considering the nutritional status.

SGA is a practical method for nutritional diagnosis. Its applicability to cirrhotic patients and to liver transplant candidates is valid, since liver disease changes the majority of objective indicators.

According to SGA, 46.5% of the patients showed a certain degree of malnutrition, and when weighed against the Child-Pugh criteria, for each unit of increase there is a 2.93 fold chance that the patient is malnourished. The other nutritional indicators did not show such strong association with the severity of liver disease. Roongpisunthinpong *et al*.[2] also reported that SGA correlates with liver disease severity, thus indicating the usefulness of SGA in patients with chronic liver disease.

An inverse correlation between disease severity and Hb, Ht and albumin was observed, regardless of the method used. The correlation of albumin levels and Child score was expected since it is used as a parameter for estimation.

Although hemoglobin and hematocrit count are independent of hepatic metabolism, they may be altered in patients with severe portal hypertension and hypersplenism as well as in the presence of gastrointestinal hemorrhages. It is noteworthy that laboratory parameters are affected by liver disease severity as well as by the etiological factors of the disease. Hence, they are more strongly correlated with disease severity than with malnutrition per se.

Although albumin synthesis depends on liver function, 51.2% of the patients presented normal albumin levels, probably related to normal liver synthesis despite the presence of cirrhosis, considering that the mean values obtained by Child-Pugh (7.11±1.7) did not characterize extremely advanced liver disease. On the other hand, as a nutritional indicator, it is relevant that 48.8% showed depleted albumin levels. This proportion was similar to the frequency of malnutrition evaluated by SGA (46.5%).

The low Child and Meld score reported in this study could raise questions regarding the indication of liver transplant in those patients. However, the values reported herein represent the values obtained in one given moment at the nutritional evaluation.

Low lymphocyte count was found in the majority of the patients, probably influenced by the presence of infection, electrolyte imbalance, renal failure, metabolic stress, inflammatory bowel diseases or immunosuppression, conditions observed in patients with liver failure and thus impairing its use as a nutritional indicator.

Currently, body composition assessment by electrical bioimpedance is considered to be a substitute or an adjunct to conventional anthropometry in research. BIA has been used in patients with cirrhosis[10] to identify those at higher mortality risk during transplantation. However, when there is an imbalance in water distribution, such as in cirrhosis, the value of single-frequency BIA to estimate body water and loan body mass may be limited.

Being aware of the limitations of single-frequency BIA in this group of patients, only the absolute values of vectors normalized by height (R/H and Xc/H) and PA were used. The great advantage by using vectors is that they are independent of regression equations and can be performed when BIA is not a valid method for estimating body composition and body fluid compartments[26,27].

PA was reduced in most of the studied population, with higher mean values in males, also demonstrated by Barbosa-Silva *et al.*[14] in 1967 healthy individuals.

A correlation of PA with disease severity was observed, and the lower the PA, greater was the disease severity, especially when assessed by the Child-Pugh criteria. Similar results were observed by Selberg and Selberg[28] in 305 cirrhotic patients and found an association of PA with the hydration state, which was lower in patients with ascites. They also noted that smaller phase angles are associated with reduced survival time.

BIA relationship with body composition is indirect and not completely understood. On the other hand, PA has been negatively correlated as a prognostic factor in many conditions such as neoplastic disease, hemodialysis, chronic obstructive pulmonary disease, HIV, including decompensate liver cirrhosis[27-29].

The correlation of vectors with severity was better with Meld criteria, and Xc/H showed the greatest correlation. Since R is inversely proportional to the amount of water, it can be suggested that females present a smaller amount of body water than males, even in liver disease.

Based on the results, it seems appropriate to use brachial measures, such as AC, AMC, AMA and those of SGA in routine outpatient care for patients with chronic liver disease. Considering the Body Composition Analysis, the absolute values of vectors and PA can also be used either for a complementary nutritional assessment or primarily for monitoring patient's clinical outcomes.

Conclusions

The diagnosis of nutritional status varied according to the method used. Body mass index was less suitable for malnutrition detection. The nutritional indicators that best correlated with the severity criteria proposed by Child-Pugh were arm circumference, arm muscle circumference, arm muscle area and global assessment of nutritional status. Single-frequency bioimpedance for body composition analysis in cirrhotic patients must be cautiously used; however, the use of primary vectors seems to be valid.

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