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Malnutrition in cirrhosis: association with etiology and hepatocellular dysfunction

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ABSTRACT – **Background** – The protein-energy malnutrition alters the prognosis of patients with cirrhosis. Its prevalence may vary according to the etiology of liver disease, it´s severity and the evaluation of the method applied. The infection by the hepatitis C virus (HCV) and alcoholism are the main etiologies of cirrhosis and result in a significant morbidity and mortality. **Objective** – To evaluate the nutritional status of patients with cirrhosis according the liver disease etiology and severity. **Methods** – It is a prospective study, in which the sample was for convenience and consisted of patients with cirrhosis, infected by HCV or alcoholic etiology. The nutritional status evaluation was carried out through anthropometry, food consumption, bioelectrical impedance (BIA) and subjective global assessment (SGA). The anthropometric data evaluated were weight, height, body mass index (BMI), triceps skinfold (TSF), circumference of the arm (CA), non-dominant handshake strength (FAM) and the adductor pollicis muscle thickness (APM). Patients were classified according to the severity of liver disease, using the Child-Pugh and Model for End-stage Liver Diseases (MELD) scores. **Results** – Ninety patients with cirrhosis were evaluated, 47 with HCV and 43 with alcoholic etiology. The prevalence of protein-calorie malnutrition ranged from 10.9% to 54.3% in the HCV group and from 4.7% to 20.9% in the alcoholic group, depending on the method used for evaluation. The group with HCV infection presented a higher malnutrition prevalence in comparison to the alcoholic in the following evaluations: TSF (P<0.001), phase angle (PA) (P=0.016) and SGA (P=0.010). PA values were lower in patients with viral cirrhosis (5.68±1.05) when compared to those with alcoholic etiology (6.61±2.31) (P=0.016). When all patients were analyzed, regardless of etiology, an inversely correlation was observed among Child-Pugh score and PA values (P=0.018). **Conclusion** – HCV cirrhosis showed worse nutritional parameters in comparison to alcoholic etiology; however, the PA was associated with worse liver function in both etiologies.

HEADINGS – Protein-energy malnutrition. Liver cirrhosis. Hepatitis C. Alcoholism.

INTRODUCTION

Patients with chronic liver disease and malnourished can have their disease prognostic and the post-transplant results modified. Malnutrition prevalence can vary according to the disease etiology, severity and evaluation method applied[1].

Identifying an ideal nutritional evaluation method for patients with cirrhosis is difficult because many of the traditional parameters like weight, body mass index (BMI) and biochemical tests can change according to the liver disease severity regardless of the nutritional condition[2,3]. Patients with cirrhosis can have their weight changed due to ascites, presence of edema and dose of diuretics. Many evaluation modalities of nutritional status have been employed, without a standard method[4].

The hepatitis C virus (HCV) infection and alcoholism are the main causes of cirrhosis with a significant morbidity and mortality. In the literature, only few studies evaluated the impact of etiology of cirrhosis in nutrition. There is a suggestion that the alcoholic disease is associated to a higher malnutrition prevalence[3,5,6]. In a recent study, we demonstrated that advanced oxidation protein products (AOPP) were elevated in the plasma of patients with cirrhosis and severe Child-Pugh classification only in the HCV etiology[7]. The knowledge of status of nutrition and its relations would predict more reliable nutritional interventions. Then, the aim of this study is to evaluate the nutritional condition of patients with cirrhosis taking into consideration the etiology and liver disease severity.

METHODS

It was a is cross-sectional study. Outpatients of a liver clinic in a tertiary hospital in South of Brazil were consecutively recruited. Criteria for inclusion were cirrhosis infected by HCV or alcoholic etiology, and age above 18 years. The study was done between September of 2015 and October of 2017.

Patients with other etiologies, those infected by immunodeficiency virus syndrome and those with neoplasia were excluded. Those receiving enteral nutrition in the last six months, the ones with hepatic encephalopathy or other clinical conditions that could disturb the food registry understanding were excluded as well. Furthermore, patients with diseases that modify the metabolism and absorption of nutrients (chronic renal insufficiency, chronic pancreatitis, chronic diarrhea, inflammatory bowel diseases) and patients with neuromuscular changes in the upper limbs or with a pacemaker or any metal material in the body that would interfere in the electrical bioimpedance values (BIA) also were excluded.

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Patients were interviewed to collect personal data and sociodemographic characteristics. The nutritional condition evaluation was performed through anthropometry, dietary intake control, BIA and subjective global assessment (SGA).

The following anthropometric measurements were analyzed: weight, height, BMI[8], triceps skinfold (TSF) and subscapular skinfold (SSF). The circumferences: abdominal (AC), waist (WC), arm (ArC) and arm muscle circumference (ArMC). The non-dominant hand grip strength (NDHGS) was measured with the mechanical dynamometer of the brand Baseline®, model Smedley Spring. The thumb adductor muscle thickness (TAMT) was obtained with the use of a Cescorf adipometer. BIA was performed with the Biodynamics appliance, model 450, version 5.1 (Biodinamics®, Corp. Seattle, WA, USA). The electric current used in the measurement was 800μA and 50 kHz what allowed measuring the resistance and reactance to find the phase angle value (PA). PA value derives from two segments of the body composition, calculated as follows: PA= arc tangent (Xc / R) x 180 / 3,1416, proposed by Barbosa-Silva et al.[9]. The cut-off point was 5.44°[10]. For the BIA evaluation, patients laid supine on a stretcher. It was placed two distal electrodes (ankle and middle toe) and two proximal electrodes (wrist and middle finger). It was asked to remove any metal prop[11,12].

The SGA used was an adaptation for liver patients[13], which combines data from the clinical history and physical examination, such as weight loss, changes in dietary intake, gastrointestinal symptoms, functional capacity, metabolic demands, indication of muscle loss and the presence of peripheral edema[14].

The food registry was carried out using a 1–125 g domestic scale (Plenna®) for food weighing, which was provided by the researchers. Patients were instructed to weigh and register all food consumed for three days (two days a week and one weekend day) in a detailed manner, including the trademark and preparation of each food and drink. Food registry was calculated using the Dietwin program. The energy average, carbohydrates, proteins and lipids, and the median of A, B1, B9, B12, D, E vitamins, zinc, magnesium, potassium, sodium, calcium, iron and phosphate were also calculated. Patients did not receive nutritional supplementation.

Patients had lab tests to check the following: magnesium, potassium, sodium, ferritin, iron, albumin, total bilirubin, prothrombin time, vitamin B12, phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), calciuria, proteinuria, creatinuria. The subjects were classified according to the liver disease severity. It was used the Child Pugh[15] classification and the Model for End-stage Liver Diseases (MELD)[16].

Regarding statistical analysis, the MsExcel 2000 program was used to store data and the statistical pack Statistical Package for the Social Science (SPSS) was used to analyze the data. The quantitative variables were presented in mean and standard deviation or median and interquartile range. To compare the means in independent samples, it was used the student-*t* test. In cases of asymmetry, the Mann-Whitney test was applied. The qualitative variables were shown as frequency and percentage. To verify the associations among these variables, the Pearson's chi-square test was applied with the complementary feature of the adjusted residue analysis to identify the associations' location. To evaluate the association among the nutritional evaluation measurements with the disease severity, the Spearman correlation test was applied. The assumed significance level was 5%.

This research was approved by the Ethics Committee. All patients signed the informed consent.

RESULTS

Ninety patients with cirrhosis were divided in two groups, one group with HCV etiology and other with alcoholic. The HCV group had 47 patients with an average age of 61.6±8.8 years; 16 (34.0%) were men and 34 (72.3%) were Caucasian. In the alcoholic group, it was evaluated 43 patients with average age of 58.5±8.6 years; 38 (88.4%) were men and 33 (76.7%) Caucasian. The most prevalent gender in patients with alcoholic etiology was the masculine (P<0.001). The majority of the patients were classified as Child-Pugh class A. There was no difference considering the liver disease severity between the groups (TABLE 1).

TABLE 1. Sample characterization (n=90).

Variables[#]	HCV group (n=47; 52.2%)	Alcohol group (n=43; 47.8%)	*P*
Age (years)	61.6±8.8	58.5±8.6	0.094
Male	16 (34.0)	38 (88.4)	<0.001
Caucasian	34 (72.3)	33 (76.7)	0.754
MELD	11.3±3.9	10.7±2.9	0.452
Child-Pugh			0.126
A	29 (63.0)	33 (78.6)	
B	15 (32.6)	6 (14.3)	
C	2 (4.3)	3 (7.1)	

#described by mean ± standard deviation, median (percentis 25–75) or n (%).
HCV: hepatitis C virus; MELD: Model for End-stage Liver Diseases.

The mean BMI was similar, 28.6 kg/m^2 and 28.9 kg/m^2, respectively (P=0.834). According to the BMI classification, 10.9% of the HCV patients and 16.3% of the alcoholic ones were malnourished. More than half of the patients from both groups were classified as overweight or obese (TABLE 2).

Analyzing the methods for nutritional diagnosis, a discrepancy was observed in the malnutrition prevalence, which varied from 10.9% to 54.3% in the HCV group and from 4.7% to 20.9% in the alcoholic group. The HCV group presented high malnutrition prevalence in comparison to the alcoholic, in the following evaluations: TST (P<0.001), PA (P=0.016) and SGA (P=0.010) (TABLE 2). It is highlighted that the PA values were lower in the patients with HCV (5.68±1.05) when compared to the alcoholic ones (6.61±2.31) (P=0.016). The macro and micronutrient values from the alcoholic group (TABLE 3) evaluated by the food registry showed: higher energy consumption (P=0.022), higher protein intake (P<0.001), vitamin B1 (P<0.001), vitamin B12 (P=0.002), vitamin D (P=0.017), calcium (P<0.001), iron (P<0.001) and phosphate (P<0.001). When analyzing the biochemical parameters, it was observed that the levels of albumin and GGT were significantly higher in the alcoholic group: (P=0.014) and (P=0.011), respectively. On the other hand, the values of AST and ALT were significantly higher in those with HCV infection: (P=0.013) and (P=0.008), respectively (TABLE 4). When all patients were analyzed, regardless of the etiology, there was an inversely association among the Child-Pugh score and PA values (P=0.018) (TABLE 5).

TABLE 6 describes the association among Child-Pugh, classes B and C, and the lower PA values (P=0.036).

TABLE 2. Anthropometric nutritional evaluation regarding cirrhosis (n=90).

Variables[#]	HCV group (n=47; 52.2%)	Alcohol group (n=43; 47.8%)	*P*
BMI (kg/m^2)	28.6±5.2	28.9±7.3	0.834
			0.683
Malnourished	5 (10.9)	7 (16.3)	
Eutrophic	13 (28.3)	8 (18.6)	
Overweight	15 (32.6)	16 (37.2)	
Obesity	13 (28.3)	12 (27.9)	
ArC			0.557
Malnourished	13 (28.3)	8 (18.6)	
Eutrophic	25 (54.3)	26 (60.5)	
Overweight /Obesity	8 (17.4)	9 (20.9)	
NDHGS			1.000
Malnourished	8 (17.4)	7 (16.3)	
Eutrophic	38 (82.6)	36 (83.7)	
TAMT			0.268
Malnourished	6 (13.0)	2 (4.7)	
Eutrophic	40 (87.0)	41 (95.3)	
TSF			<0.001
Malnourished	25 (54.3)*	8 (18.6)	
Eutrophic	9 (19.6)	6 (14.0)	
Overweight/obesity	12 (26.1)	29 (67.4)*	
PA	5.68±1.05	6.61±2.31	0.016
			0.050
Malnourished	17 (37.0)	7 (16.3)	
Eutrophic	29 (63.0)	36 (83.7)	
SGA			0.010
Malnourished	18 (38.3)*	9 (20.9)	
Well-nourished	29 (61.7)	34 (79.1)	

[#] Described by mean ± standard deviation or n (%). * Statistically significant association by the residuals test adjusted to the significance of 5%.
HCV: chronic hepatitis C virus; BMI: body mass index; ArC: arm circumference; NDHGS: non-dominant hand grip strength; TAMT: thumb adductor muscle thickness; TSF: triceps skinfold thickness; PA: phase angle; SGA: subjective global assessment.

TABLE 3. Food consumption of patients with cirrhosis (n=90).

Variables*	HCV group (n=47; 52.2%)	Alcohol group (n=43; 47.8%)	*P*
Energy	1699±515	1960±541	0.022
CHO	264.4±86.6	293.1±95.3	0.141
PTN	80.7±35.1	112±34.9	<0.001
LIP	35.3±16.4	40.4±19.3	0.181
VITB1	1.37 (0.79–2.06)	2.44 (1.51–3.03)	<0.001
VITB9	73.5 (34.2–117.5)	79.2 (49.7–105)	0.755
VITB12	0.74 (0.08–2.64)	2.59 (0.80–5.05)	0.002
VITA	327 (109–867)	214 (68.6–461)	0.153
VITD	0.45 (0.06–0.88)	0.71 (0.46–1.51)	0.017
VITE	8.39 (2.29–14.6)	7.81 (3.18–12.1)	0.780
Zinc	4.82 (1.72–9.04)	6.64 (3.58–9.69)	0.117
Magnesium	119.8 (72–165.6)	96.3 (77.8–128.1)	0.304
Potassium	1134 (801–1648)	1088 (859–1599)	0.895
Sodium	1245 (717–1818)	1251 (845–1679)	0.527
Calcium	344 (170–604)	618.5 (481–969)	<0.001
Iron	13.7 (7.8–22.6)	24.9 (19.2–33.4)	<0.001
Phosphate	805 (501–1184)	1249 (1003–1689)	<0.001

* Described by mean ± standard deviation or median (percentis 25–75).
HCV: chronic hepatitis C virus; CHO: carbohydrates, PTN: proteins, LIP: lipids, VITB1: vitamin B1, VITB9: vitamin B9, VITB12: vitamin B12, VITA: vitamin A, VITD: vitamin D, VITE: vitamin E.

TABLE 4. Cirrhosis patients biochemical parameters (n=90).

Variables*	HCV group (n=47; 52.2%)	Alcohol group (n=43; 47.8%)	*P*
Vitamin B12	610.2±245.8	610.8±254.5	0.991
Magnesium	1.98±0.22	1.95±0.28	0.491
Potassium	4.42±0.51	4.60±0.39	0.059
Sodium	140.3±2.71	137.1±19.4	0.259
Phosphate	3.46±0.52	3.43±0.49	0.782
Iron	125.2±55.1	104.4±44.6	0.054
Ferritin	168 (62–391)	176 (82–286)	0.913
Total Bilirubin	1.4 (0.6–2.1)	1.1 (0.8–1.9)	0.590
NIR*	1.26±0.26	1.22±0.16	0.379
Albumin	3.74±0.64	4.04±0.50	0.014
Calciuria	120 (85.3–190.3)	116 (70.5–206)	0.837
Proteinuria	0.11 (0.06–0.19)	0.09 (0.05–0.15)	0.510
Creatinuria	1.05±0.49	1.23±0.59	0.139
CI	0.069±0.027	0.067±0.032	0.803
AST	57.5 (30.5–102)	38 (27.7–48.5)	0.013
ALT	43 (24.3–70.3)	28.5 (20.8–36.5)	0.008
APH	114.7±43.6	117.7±47.2	0.760
GGT	59 (33–101)	101 (51–169)	0.011

* Described by mean ± standard deviation or median (percentis 25-75) or n (%).
HCV: chronic hepatitis C virus; NIR: international normalized ratio, CI: creatinine index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, APH: alkaline phosphatase, GGT: gamma-glutamyltranspeptidase.

TABLE 5. Associations of PA and SGA measurements with the disease severity in patients with cirrhosis (n=90).

Variables	PA		SGA	
	Spearman correlation coefficient	*P*	Spearman correlation coefficient	*P*
MELD	-0.193	0.080	-0.012	0.916
Child-Pugh	-0.254	0.018	0.139	0.197

PA: phase angle; SGA: subjective global assessment; MELD: Model for End-stage Liver Diseases.

TABLE 6. Associations between SGA and PA with the Child-Pugh classification in patients with cirrhosis (n=88).

Variables	Child-Pugh A (n=62; 70.5%)	Child-Pugh B + C (n=26; 29.5%)	*P*
SGA			0.081
Well-nourished	46 (74.2)	15 (57.7)	
Moderately malnourished	13 (21.0)	11 (42.3)	
Severely malnourished	3 (4.8)	0 (0.0)	
PA	6.42±2.04	5.53±1.03	0.036
			0.054
Malnourished	12 (19.7)	11 (42.3)	
Eutrophic	49 (80.3)	15 (57.7)	

SGA: subjective global assessment; PA: phase angle.

DISCUSSION

Prevalence of malnutrition in this study differed considering the method applied, ranging from 10.9% to 54.3% in patients with HCV and from 4.7% to 20.9 % in alcoholic patients. In literature, protein-energy malnutrition is a common condition in patients with cirrhosis and is considered an independent survival predictor[17,18]. On the other hand, there is not a nutritional evaluation method considered as standard.

SGA has been used for the evaluation of patients with chronic liver disease and is described as an efficient method to predict the malnutrition[13,19,20]. In the present study, a correlation between SGA and liver disease severity was not observed. Barcelos et al., demonstrated the association between the SGA and Child-Pugh C classification[21].

Regarding PA, literature highlights its importance in the evaluation of a patient with chronic liver disease[22]. A study carried out in our group defined the PA cutoff point in this population of patients, showing its correlation with the prognostic[10].

Bering et al. evaluated 135 patients with HCV infection, comparing the PA value between the cirrhosis patients and the ones without severe fibrosis. The authors showed a statistically significant difference of a lower PA in patients with cirrhosis. This low PA was linked to malnutrition[23]. Dorna et al. also demonstrated the association between PA and advanced fibrosis in HCV patients. As the PA degrees decreased, the risk of developing advanced fibrosis increased over four times[24]. Ruiz-Margáin et al. assessed 249 patients with compensated cirrhosis in a prospective cohort study with a 48-month follow-up period. The PA cutoff point for malnutrition was lower than or equal to 4.9 degrees. This study also concluded that the PA is a good prognostic marker[25].

Considering nutritional differences in different etiologies of chronic liver disease, the current study showed high malnutrition prevalence and lower PA value in HCV patients, what is in opposition to some studies that suggested worse nutritional condition in alcoholic patients[26-28]. One of the possible explanations is the prevalent divergence regarding the applied method. In a study by Vulcano et al., the major prevalence of malnutrition in a subgroup of alcoholic patients was shown only when arm muscle circumference (ArMC) and arm circumference (ArC) were evaluated[29].

In our study, the energy consumption, proteins, vitamins B1, B12, D, calcium, iron and phosphate were statistically higher in the alcoholic group. In the same way, it was observed that the albumin (P=0.014) was higher in patients with alcoholic etiology. Calorie intake, especially proteins, is associated to the nutritional condition[30-32]. Other authors did not find differences in relation to malnutrition and the liver disease etiology[6,33].

In this study, it was observed an inverse association between Child-Pugh and PA. However, this association was not shown in relation to the MELD, which evaluates the international normalized ratio (INR), creatinine and total bilirubin. Contrary to MELD, the Child-Pugh evaluates the presence of ascites and albumin values, which are frequently associated to malnutrition. Ferreira et al. did not find a correlation between the disease's severity and the MELD score[34].

Selberg and Selberg, showed worse survival in patients with cirrhosis for those with PA smaller or equal to 5.4º and even worse prognosis when PA was smaller than 4.4º[35]. In the same way, Barbosa-Silva et al. evidenced a correlation between PA and disease severity evaluated by Child-Pugh classification[9].

Belarmino et al. showed that PA ≤4.9º predicted the death of male cirrhotic patients in a model adjusted to age and MELD score. According to Belarmino et. al., this cutoff point was able to identify patients with significant changes in inflammatory and nutritional markers, which are highly indicative of catabolism and malnutrition[36]. It is important to emphasize that PA values can change due to nutritional interventions because it has more sensitive than other nutritional markers[37].

Considering the anthropometric variables used in the present study, only the TSF agreed with the results of SGA and PA, demonstrating a higher malnutrition prevalence in HCV. Nunes et al. suggested that TST appears to be the most efficient anthropometric parameter to assess nutritional status in these patients and is clearly associated with a poorer prognosis[38].

The present study has some limitations; the small sample, the lack of standard method to define malnutrition in patients with cirrhosis and the restrictions of the procedures used, specially the evaluation of nutritional status by anthropometry in patients with end stage liver disease.

In conclusion, this study demonstrated worse nutritional status in patients with cirrhosis and hepatitis C. On the other hand, PA was a good method to assess prognosis and could represent an additional tool to the ordinarily used parameters to evaluate liver disease severity and nutritional intervention.

Authors' contribution

Coral GP, Fernandes SA and Oliveira KS conceptualized the study. Oliveira KS and Oliveira LR collected the data. Oliveira KS, Oliveira LR, Fernandes SA and Coral GP analysed the data and wrote the manuscript. All the authors revised and approved the final version.

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RESUMO – **Contexto** – A desnutrição proteico-calórica altera o prognóstico dos pacientes com cirrose. Sua prevalência pode variar de acordo com a etiologia da hepatopatia, gravidade da doença e o método de avaliação empregado. A infeção pelo vírus da hepatite C (VHC) e o alcoolismo, estão entre as principais etiologias da cirrose e acarretam significativa morbidade e mortalidade. **Objetivo** – Avaliar o estado nutricional do paciente com cirrose de acordo com a etiologia e gravidade da hepatopatia. **Métodos** – Estudo prospectivo, em que a amostra foi por conveniência constituída de pacientes com cirrose, infectados pelo vírus da hepatite C (VHC) ou etiologia alcoólica. A avaliação do estado nutricional foi realizada através da antropometria, consumo alimentar, bioimpedância elétrica (BIA) e da avaliação subjetiva global (ASG). Os dados antropométricos avaliados foram: peso, altura, índice de massa corporal (IMC), prega cutânea triciptal (PCT), circunferências do braço (CB), força do aperto de mão não dominante (FAM) e a espessura do músculo adutor do polegar (MAP). Os pacientes foram classificados de acordo com a gravidade da hepatopatia, através do escore Child-Pugh e *Model for End-stage Liver Diseases* (MELD). **Resultados** – Foram avaliados 90 pacientes com cirrose, 47 com etiologia pelo VHC e 43 com etiologia alcoólica. A prevalência de desnutrição proteico-calórica variou de 10,9% a 54,3% no grupo do VHC e de 4,7% a 20,9% no grupo dos alcoolistas, dependendo do método utilizado para avaliação. O grupo com infecção pelo VHC apresentou maior prevalência de desnutrição em relação ao de etiologia alcoólica nas seguintes avaliações: PCT (P<0,001), ângulo de fase (AF) (P=0,016) e ASG (P=0,010). Os valores do AF foram menores nos pacientes com cirrose viral (5,68±1,05) quando comparados aos com etiologia alcoólica (6,61±2,31) (P=0,016). Quando analisados todos os pacientes, independente da etiologia da hepatopatia, observou-se uma correlação inversamente proporcional entre a classificação de Child-Pugh e os valores de AF (P=0,018). **Conclusão** – A cirrose pelo VHC demonstrou piores parâmetros nutricionais em relação à etiologia alcoólica; entretanto, em ambas etiologias o AF foi associado com pior função hepática em ambas etiologias.

DESCRITORES – Desnutrição proteico-calórica. Cirrose hepática. Hepatite C. Alcoolismo.

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