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Malnutrition assessed through phase angle and its relation to prognosis in patients with compensated liver cirrhosis: A prospective cohort study

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ABSTRACT

Background: Malnutrition is a frequent complication of cirrhosis and it has been associated to more severe disease and development of complications. Phase angle is a bedside reliable tool for nutritional assessment based on conductivity properties of body tissues.
Aim: To evaluate the association between malnutrition assessed through phase angle and mortality in patients with liver cirrhosis.
Methods: We performed a prospective cohort study in a tertiary care centre; 249 patients were enrolled with 48 months of follow-up. Clinical, nutritional (malnutrition = phase angle $\leq 4.9^{\circ}$) and biochemical evaluations were performed. Student's *t*-test and χ^2 method were used as appropriate. Kaplan–Meier curves and multivariate Cox regression were used to evaluate mortality.
Results: Mean follow-up was 33.5 months. Survival analysis showed higher mortality in the malnourished group compared to the well-nourished group ($p = 0.076$), Kaplan–Meier curves were further stratified according to compensated and decompensated status showing higher mortality in compensated patients according to Child–Pugh ($p = 0.002$) and Model for End-Stage Liver Disease score ($p = 0.008$) when malnutrition was present. Multivariate analysis showed that malnutrition was independently associated with mortality (HR = 2.15, 1.18–3.92).
Conclusions: In our cohort, malnutrition was independently associated with mortality. This is the first study showing higher mortality in malnourished compensated cirrhotic patients.

1. Introduction

Several studies have shown that malnutrition in cirrhosis is associated with higher mortality, and it has an impact on surgical and post-transplantation outcomes. Also, the major life-threatening complications of cirrhosis including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome, have all been shown to be affected by malnutrition and sarcopenia [1–5]. Despite the importance of nutritional status in patients with liver cirrhosis there is no gold standard for nutritional assessment [6].

Bioelectrical impedance analysis (BIA) based on the conductivity properties of the body tissues has been used in cirrhosis for nutritional assessment, as it has been shown to be a useful bedside method for this purpose with some limitations in patients with fluid retention [7]. The main limitations of BIA in patients with fluid retention are observed when prediction equations are used to obtain estimated markers of body composition (i.e. fat mass, fat free mass) mainly because this equations are based on healthy population. Phase angle (PhA) is a nutritional marker obtained directly from (BIA) and it is one of the direct measurements that is not subjected to prediction equations and it reflects a relation between resistance and reactance, also direct measurements of BIA Resistance measures the opposition from cellular membranes and reactance measures the opposition from body fluids to the current. Therefore, phase angle indicates both, integrity of cellular membranes and water cellular distribution, which reflect nutritional status [5,8,9,12].

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PhA is a nutritional status marker of great clinical relevance that can be used as a tool to establish an early nutritional treatment in the patient, and thus reducing the development of complications, hospital length of stay and improving survival. Likewise it can be used as a complement for other nutritional screenings [9,11,13,14].

Recently, a few PhA cut-off points have been proposed to define malnutrition in cirrhosis, and found to be useful in predicting severe disease and mortality. Since evidence is still limited and PhA needs specific validation in different ethnic groups [10,11,13,14].

We aimed to evaluate the relation between malnutrition assessed through PhA and mortality in patients with liver cirrhosis.

2. Materials and methods

2.1. Methods

This was a prospective cohort study. Patients attending gastroenterology and hepatology clinics at a third-level hospital in Mexico City (Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán") between March 2009 and June 2010 were screened for study enrolment.

This study was designed and conducted according to the principles of the Declaration of Helsinki and was approved by the local Institutional Ethics Committee (*CIIBH Comité de ética en Investigación INCMNSZ*). Informed consent was obtained from each participant (ClinicalTrials.gov NCT02023177).

All of the authors had access to the study data, reviewed and approved the final manuscript.

2.2. Primary endpoint

The primary endpoint was mortality. Possible confounding factors were disease severity as assessed by Child–Pugh and MELD score, age, gender, and cirrhosis-related complication, which were evaluated for posterior statistical analysis.

2.3. Inclusion criteria

We included patients between 18 and 65 years, with a diagnosis of cirrhosis based on the combination of clinical features, radiological imaging, presence of portal hypertension, compatible biochemical parameters, and/or confirmatory liver biopsy. Inclusion was not restricted by aetiology of cirrhosis.

2.4. Exclusion criteria

We excluded patients with acute or chronic renal failure, patients that had undergone major surgery in the four weeks before recruitment, pregnancy, active alcoholism and patients with acute disease, such as infections, and patients with extremity amputation.

2.5. Evaluation of participants

The follow-up consisted of 48 months and each participant was evaluated 5 times. All patients had clinical and nutritional evaluation that consisted of the following anthropometrical, clinical and biochemical methods.

2.6. Clinical evaluation

Physical examination was performed in each patient to evaluate the presence of ascites, oedema and hepatic encephalopathy.

Disease severity was established according to Child–Pugh (CP) and MELD score (Model for End-Stage Liver Disease).

Decompensation was defined as CP $\geq$ 7 and MELD score $\geq$ 14 [22,23].

2.6.1. Anthropometry

Weight and height were measured in each patient. With these measurements we calculated BMI as weight/height squared (kg/m^2).

2.7. Bioelectrical impedance

BIA was performed using RJL systems Quantum IV (Clinton Township, MI, USA) applying alternating electric currents of 800 μA at 50 kHz with the aid of Ag/AgCl source and sensor electrodes to obtain R, Xc and phase angle (i.e. the arc tangent of the ratio of reactance to resistance transformed to degrees). BIA was performed after an overnight fasting in supine position with arms and legs abducted from the body [15]. Source and sensor electrodes were placed on the dorsum of both hand and foot on the right side of the body, respectively.

2.8. Phase angle

Phase angle cut-off was obtained from a pilot study, using area under ROC yielding 4.9° as the best cut-off for malnutrition associated to severity of the disease (Unpublished data). In this study malnutrition was defined as PhA $\leq$ 4.9°.

2.9. Biochemical tests

Biochemical tests including serum albumin, creatinine, sodium, liver function tests, prothrombin time and INR were obtained within the first week of study enrolment.

2.10. Statistical analysis

Sample size was calculated in order to provide 80% power and α error of 0.05, considering a difference of proportions of mortality of 20% with 15% anticipated loss of follow-up, and stratifying by disease severity a priori, the calculation yielded 221 patients.

Clinical, nutritional and biochemical variables are presented as mean ± SD for quantitative variables; proportions and frequencies were used for categorical variables. Kolmogorov–Smirnov normality test was performed for quantitative variables. Quantitative variables are presented as mean ± SD and difference between groups was assessed by Student's *t*-test; and for categorical variables are presented as proportions and χ^2 method was used. Kaplan–Meier curves and log-rank test were used to evaluate mortality, followed by multivariate Cox regression. Missing data were excluded from analysis and in the case of Kaplan–Meier curves; censored cases are included in the curves.

Statistical analysis was carried out using the software package SPSS version 21 (IBM, Armonk, NY).

3. Results

3.1. Baseline characteristics

The total population consisted of 249 patients; the inclusion of patients is shown in Fig. 1. The mean follow-up of patients was 33.5 months, with 8 months as minimum, up to 48 months as maximum follow-up time. A total of 62 deaths were reported and analysed.

Nutritional status of each participant was established at the end of follow-up according to PhA and patients were included in one of two groups Malnourished (PhA $\leq$ 4.9°) and Well-nourished (PhA > 4.9°); baseline clinical and demographic characteristics of these groups are presented in Table 1. In the Malnourished group