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

Astrid Ruiz-Margáin[a], Ricardo U. Macías-Rodríguez[a], Andrés Duarte-Rojo[c], Silvia L. Ríos-Torres[a], Ángeles Espinosa-Cuevas[b], Aldo Torre[a,*]

[a] Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", México, D.F., Mexico
[b] Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", México, D.F., Mexico
[c] Division of Gastroenterology and Hepatology, University of Arkansas for Medical Sciences, Little Rock, AR, United States

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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 $\chi^2$ 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].

* Corresponding author at: Vasco de Quiroga 15, Col. Sección XVI, Tlalpan, 14000 México, D.F., Mexico. Tel.: +52 55 54870900x2711.
*E-mail address:* detoal@yahoo.com (A. Torre).

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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 $\alpha$ 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 $\chi^2$ 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

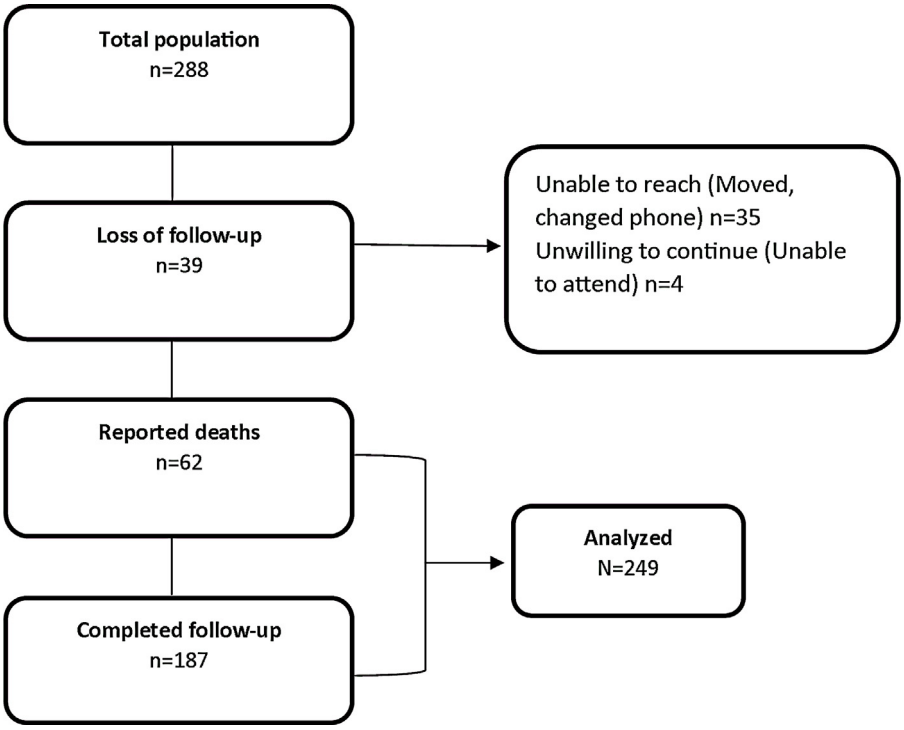


**Fig. 1.** Enrollment and follow-up of the study population.

**Table 1**
Demographic, clinical and biochemical characteristics of the study population according to nutritional status.

| | Malnourished ($n=133$) | Well-nourished ($n=116$) | *P* value |
|---|---|---|---|
| Age (years) | 51.98 ± 10.98 | 53.13 ± 11.49 | 0.416 |
| Weight (kg) | 69.54 ± 16.53 | 70.03 ± 16.85 | 0.819 |
| BMI (kg/m$^2$) | 27.75 ± 6.12 | 26.86 ± 5.04 | 0.21 |
| TSF | 22.01 ± 7.31 | 23.47 ± 8.26 | 0.387 |
| MAMC | 21.89 ± 3.22 | 25.75 ± 3.71 | 0.000 |
| Resistance (ohms) | 536.1 (472.25–620) | 496.5 (442–556.5) | 0.000 |
| Reactance (ohms) | 39.84 ± 9.6 | 52.29 ± 9.9 | 0.000 |
| Child–Pugh (points) | 8 (7–10) | 7 (5–8) | 0.000 |
| MELD score | 12.5 (9–14.9) | 11 (8–14) | 0.086 |
| Creatinine (mg/dL) | 0.735 (0.3–0.95) | 0.79 (0.67–0.91) | 0.255 |
| Total bilirrubin (mg/dL) | 2 (1.2–3.67) | 1.7 (1.1–2.67) | 0.012 |
| Albumin (mg/dL) | 3.10 ± 0.58 | 3.01 ± 0.69 | 0.130 |
| Ammonia (mcg/dL) | 75 (45.6–117.2) | 66.8 (42.4–94.7) | 0.323 |
| INR | 1.39 ± 0.40 | 1.19 ± 0.26 | 0.110 |
| Ascites | 33.60% | 29.80% | 0.546 |
| Oedema | 27.40% | 25.00% | 0.687 |
| Hepatic encephalopathy | 20.50% | 21.40% | 0.878 |
| Esophageal varices | 80.00% | 77.80% | 0.73 |

BMI, body mass index; TSF, triceps skinfold thickness, MAMC, mid-arm muscle circumference, MELD, Model for End Stage Liver Disease; INR, international normalized ratio.

BMI, total bilirubin, albumin and ammonia levels were higher compared to the well nourished group however there was no statistical significance.

### 3.2. Malnutrition

The frequency of malnutrition in the total population was 54%. In compensated patients according to Child–Pugh malnutrition was present in 37% of the patients, and according to MELD score 50% of the patients were malnourished. In decompensated patients malnutrition increased to 71% and 60%.

### 3.3. Survival in the total population

In the total population mean survival for well-nourished patients was 42.09 (95% CI: 39.91–44.27) compared to malnourished patients 39.18 (95% CI: 36.51–41.85). The 4-year probability of survival in the well-nourished group was 81.5% compared to 72.3% in the malnourished group although this difference was not statistically significant ($p=0.076$).

The main causes of death were variceal bleeding (39.1%), infections (30.4%), hepatocellular carcinoma (21.7%) and others (8.8%).

### 3.4. Survival in compensated patients

When groups were stratified according to compensated status, curves showed higher survival in well-nourished patients. In compensated patients according to Child–Pugh mean survival was 43.6 months (95% CI: 41.2–46.0) in well-nourished patients and 35.9 months (95% CI: 30.7–41.0) in malnourished patients; 4-year survival was 86.2% and 63.2% respectively.

In compensated patients according to MELD score mean survival was 43.9 months (95% CI: 41.69–46.24) in well-nourished patients and 39 months (95% CI: 35.8–42.2) in malnourished patients; 4-year survival was 86.6% and 71.1% respectively (Fig. 2).

### 3.5. Survival in decompensated patients

Survival curves according to decompensated status showed no difference in survival between well-nourished and malnourished groups. In decompensated patients according to Child–Pugh mean survival was 39.4 months (95% CI: 34.8–43.8) in well-nourished patients and 40.4 months (95% CI: 37.3–43.5) in malnourished patients; 4-year survival was 71.8% and 75.9% respectively ($p=0.791$).

In decompensated patients according to MELD score mean survival was 34.3 months (95% CI: 27.3–41.3) in well-nourished

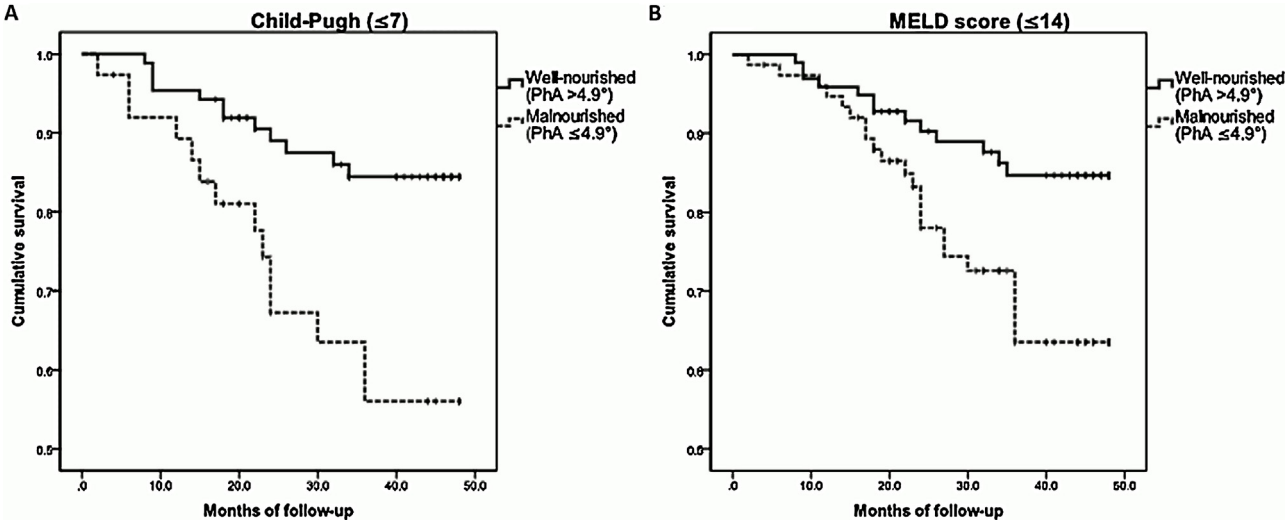


**Fig. 2.** Survival curves of well-nourished patients (phase angle > 4.9°) compared to malnourished patients (phase angle ≤ 4.9°) in compensated patients according to Child–Pugh (A) [Log rank $p = 0.002$] and MELD score (B) [Log rank $p = 0.008$].

**Table 2**
Characteristics associated to mortality in univariate Cox analysis.

| Variable | HR | 95% confidence interval | *P* value |
|---|---|---|---|
| Gender (Female) | 0.47 | 0.28–0.80 | **0.005** |
| Age (>55 years) | 1.01 | 0.98–1.03 | 0.729 |
| Child–Pugh > 7 points | 0.84 | 0.5–1.43 | 0.529 |
| MELD score >14 points | 2.04 | 1.15–3.60 | **0.014** |
| Phase angle (≤4.9°) | 1.58 | 0.93–2.74 | **0.091** |
| Mild ascites | 0.76 | 0.39–1.48 | 0.417 |
| Moderate ascites | 1.52 | 0.49–4.72 | 0.468 |
| Severe ascites | 2.71 | 0.87–8.41 | **0.084** |
| Presence of esophageal varices | 0.92 | 0.39–2.15 | 0.851 |
| Grade I HE | 1.14 | 0.45–2.88 | 0.783 |
| Grade II HE | 1.10 | 0.29–4.09 | 0.887 |

MELD, Model for End Stage Liver Disease; HE, hepatic encephalopathy.

**Table 3**
Characteristics associated to mortality in multivariate Cox regression analysis.

| Variable | HR | 95% confidence interval | P value |
|---|---|---|---|
| Phase angle (≤4.9°) | 2.15 | 1.18–3.92 | 0.024 |
| MELD score >14 points | 1.51 | 1.20–4.30 | 0.041 |
| Severe ascites | 2.04 | 1.10–6.76 | 0.027 |
| Gender (male) | 1.59 | 0.92–2.72 | 0.091 |

MELD, Model for End Stage Liver Disease.

patients and 35.4 months (95% CI: 28.30–42.6) in malnourished patients; 4-year survival was 57.1% and 65.4% respectively ($p = 0.694$)

### 3.6. Characteristics associated with mortality

To determine the variables that would be included in the multivariate analysis we performed a univariate analysis and we established that variables with a significance value <0.20 would be included. Table 2 shows the results of univariate analysis; variables significance level <0.20 (*P* value in bold) were gender, MELD score, phase angle and severe ascites.

In the multivariate Cox regression model, PhA remained associated to mortality with a HR of 2.15, MELD score and severe ascites also remained associated to mortality (Table 3).

## 4. Discussion

As liver disease progresses complications begin to appear such as variceal bleeding, ascites and hepatic encephalopathy; the presence of these factors is associated with mortality. In addition to these factors, other risk factors have been proposed such as malnutrition, sarcopenia, presence of infection, chronic inflammation, among others [16–18].

Malnutrition is an important complication of cirrhosis, and it occurs more frequently than other complications such as ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome among others, and still it remains underdiagnosed [19].

Nutritional assessment in cirrhosis represents a major challenge for the clinician due to the main characteristics of the disease such as fluid retention (malnutrition is underestimated by anthropometric methods), hypersplenism (error in the evaluation of biochemical parameters such as lymphocytes) and hepatic encephalopathy (inability to perform the evaluation test by dynamometry) [20]. Some algorithms for the assessment of nutritional status in cirrhosis are based on body mass index (BMI), and, according to previous literature, in our study there was no difference in weight between well-nourished and malnourished patients.

There is evidence that suggest that nutritional assessment methods such as BIA and precisely bioelectrical impedance vector analysis (BIVA) are more accurate than other proposed to date [14,15]. The data provided by the bioelectrical impedance analysis are reactance (Xc), resistance (R) and phase angle PhA [21]. The importance of these variables is that they are direct measurements not subject to error and post-analysis. Specifically, the PhA obtained from BIA is a parameter that has been associated with prognosis in different diseases such as HIV, cancer and heart failure, among others. It has been established that lower levels of PhA are associated with increased morbidity and mortality [4,9,10,17].

There are few studies including PhA in patients with cirrhosis; these studies in Brazilian and German populations have proposed PhA values of 5.18°, 5.4° and 5.44° respectively and have shown a relation to severity of the disease, and mortality when controlling for age and other nutritional variables [11,14]. In this study the cutoff of PhA used to define malnutrition was obtained in relation to the severity of the disease yielding 4.9° in a pilot study, this cutoff was then used to establish malnutrition in this cohort of cirrhotic patients, showing that PhA holds a good predictive validity, given that it is able to predict mortality, which represents the most

solid outcome, and therefore this cut-off is now validated in our population.

We found no significant difference between the characteristics of malnourished and well-nourished groups we can presume that, since the groups are homogeneous, mortality can be attributed to malnutrition.

When survival analysis was performed, the Kaplan–Meier curves in the total population showed a significant, although modest, difference between well-nourished and malnourished groups. This difference became larger when Kaplan–Meier curves were stratified according to severity status assessed by Child–Pugh and MELD score. An interesting finding was that compensated patients according to both scales showed higher mortality when malnutrition was present, but this difference was not present in decompensated patients, where the curves showed no difference in mortality between malnourished and well-nourished patients. We speculate that the results seen in compensated patients could be explained by the impact of malnutrition in the increased incidence of complications and worse outcome after the development of cirrhosis-specific complications, and in the decompensated group the presence of multiple complications could be disguising the impact of malnutrition.

All patients were included in the multivariate Cox regression analysis; results showed that malnutrition assessed through PhA $\leq 4.9^{\circ}$ was independently associated with mortality when controlling for gender, and severity of the disease. We evaluated other Cox regression models that included aetiology but we did not find an association to mortality (data not shown).

Previous studies have evaluated malnutrition and mortality; these studies have used various methods for nutritional assessment such as CT scan, subjective global assessment, mid-arm muscle circumference and clinical evaluation; the design and follow-up time of these studies have varied widely making them very heterogeneous. Some studies suggest that malnutrition is strongly related to mortality and cirrhosis-related complications and other few studies suggest that there is no such association [5,6,10,11,14,16].

To our knowledge this is the first study showing an association between malnutrition and mortality in compensated cirrhosis. The implications of this finding are of great importance. Classically, prognosis in cirrhosis is related to portal hypertension and to hepatocellular function. Beyond these two factors, nutritional status plays an important role in cirrhosis. The fact that malnutrition was related to mortality only in compensated patients could be explained because the effect of malnourishment could be blunted for other complications in decompensated patients such as sepsis, variceal haemorrhage and hepatocellular carcinoma.

The possible limitations of this study are that our results could be limited to our population, the fact that the patients were from a third level referral centre so applicability to general population could be limited, therefore further studies are needed to validate these results.

In summary our findings show that malnutrition is an important complication of cirrhosis and it has an impact on the prognosis of cirrhotic patients when other cirrhosis-related complications are not present such as hepatic encephalopathy and ascites. Therefore it is of great importance to provide nutritional support for these patients, such as dietary guidance and even supplementation with branched-chain amino acids in early stages of the disease to improve the outcome in cirrhosis [24–27].

In conclusion, in our cohort of cirrhotic patients malnutrition (PhA $\leq 4.9^{\circ}$) was independently associated with mortality. This is the first study showing higher mortality in malnourished compensated cirrhotic patients. Implementation of PhA could be a useful and reliable bedside tool to evaluate prognosis in compensated cirrhosis.

## Conflict of interest

None declared.

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