

World Journal of *Methodology*

World J Methodol 2023 September 20; 13(4): 166-372



EDITORIAL

- 166 Importance of methodological considerations in documenting psychological trauma
Vyshka G, Elezi F, Mana T

OPINION REVIEW

- 170 ChatGPT in action: Harnessing artificial intelligence potential and addressing ethical challenges in medicine, education, and scientific research
Jeyaraman M, Ramasubramanian S, Balaji S, Jeyaraman N, Nallakumarasamy A, Sharma S

REVIEW

- 179 Compensated liver cirrhosis: Natural course and disease-modifying strategies
Kumar R, Kumar S, Prakash SS
- 194 Telemedicine in inflammatory bowel diseases: A new brick in the medicine of the future?
Gravina AG, Pellegrino R, Durante T, Palladino G, D'Onofrio R, Mammone S, Arboretto G, Auletta S, Imperio G, Ventura A, Romeo M, Federico A

ORIGINAL ARTICLE**Basic Study**

- 210 Utilization of online systems to promote youth participation in research: A methodological study
Salem M, Pollack L, Zepeda A, Tebb KP
- 223 Comprehensive analysis of cell-extracellular matrix protein Ras suppressor-1 in function and prognosis of gastrointestinal cancers
Xu Y, Hou YY, Wu Z, Fang ZX, Wu HT, Liu J

Retrospective Cohort Study

- 238 Role of the phase angle in the prognosis of the cirrhotic patient: 15 years of follow-up
Pinto LP, Marroni CA, Czermainski J, Dahlem MLF, Carteri RB, Fernandes SA

Retrospective Study

- 248 Association of carbon monoxide poisonings and carboxyhemoglobin levels with COVID-19 and clinical severity
Coskun A, Demirci B, Turkdogan KA

Observational Study

- 259 External validation of the Moroccan Arabic version of the European Organization for Research and Treatment of Cancer colorectal (CR29) module: Monocentric study
Bachri H, Essangri H, El Bahaoui N, Benkabbou A, Mohsine R, Majbar AM, Souadka A

- 272 Biliary fistula and late recurrence of liver hydatid cyst: Role of cysto-biliary communication: A prospective multicenter study

Habeeb TAAM, Podda M, Tadic B, Shelat VG, Tokat Y, Abo Alsaad MI, Kalmoush AE, Nassar MS, Mustafa FM, Morsi Badawy MH, Sobhy Shaaban M, Mohamed TZ, El Sayed Henish MI, Elbelkasi H, Abdou Yassin M, Mostafa A, Ibrahim A, A-Abdelhady W, Elshahidy TM, Mansour MI, Moursi AM, Abdallah Zaitoun M, Abd-Allah ES, Abdelmonem Elsayed A, S Elsayed R, M Yehia A, Abdelghani A, Negm M, Abo-Alella HA, Elaigy MM

Prospective Study

- 287 Role of endoscopic ultrasound and endoscopic ultrasound-guided tissue acquisition in diagnosing hepatic focal lesions

Okasha HH, Delsa H, Alsawaf A, Hashim AM, Khattab HM, Abdelfatah D, Abdellatef A, Albitar A

SYSTEMATIC REVIEWS

- 296 Post-COVID-19 cholangiopathy: Systematic review

Rasheed MA, Ballotin VR, Bigarella LG, Soldera J

- 323 Potential long-term neurological and gastrointestinal effects of COVID-19: A review of adult cohorts

Sherif ZA, Deverapalli M, Challa SR, Martirosyan Z, Whitesell P, Pizuorno AM, Naqvi Z, Tulloch IK, Oskrochi G, Brim H, Ashktorab H

SCIENTOMETRICS

- 337 Physician-scientists or celebrities? Kardashian-index of gastroenterologists

Ugonabo O, Malik SU, Akbar UA, Zamani Z, Frandah W

- 345 Mapping research trends of transarterial chemoembolization for hepatocellular carcinoma from 2012 to 2021: A bibliometric analysis

Zhang N, He XF, Niu XK

CASE REPORT

- 359 Clinical, imaging, arthroscopic, and histologic features of bilateral anteromedial meniscofemoral ligament: A case report

Luco JB, Di Memmo D, Gomez Sicre V, Nicolino TI, Costa-Paz M, Astoul J, Garcia-Mansilla I

- 366 Sclerotic marginal zone lymphoma: A case report

Moureiden Z, Tashkandi H, Hussaini MO

ABOUT COVER

Peer Reviewer of *World Journal of Methodology*, Ahmad Ozair, MBBS, Postdoctoral Fellow, Miami Cancer Institute, Baptist Health South Florida, Miami, FL 33176, United States. ahmad.ozair@baptisthealth.net

AIMS AND SCOPE

The primary aim of *World Journal of Methodology* (*WJM*, *World J Methodol*) is to provide scholars and readers from various fields of methodology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJM mainly publishes articles reporting research results obtained in the field of methodology and covering a wide range of topics including breath tests, cardiac imaging techniques, clinical laboratory techniques, diagnostic self-evaluation, cardiovascular diagnostic techniques, digestive system diagnostic techniques, endocrine diagnostic techniques, neurological diagnostic techniques, obstetrical and gynecological diagnostic techniques, ophthalmological diagnostic techniques, otological diagnostic techniques, radioisotope diagnostic techniques, respiratory system diagnostic techniques, surgical diagnostic techniques, *etc.*

INDEXING/ABSTRACTING

The *WJM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Zi-Hang Xu, Production Department Director: Xu Guo, Editorial Office Director: Ji-Hong Liu.

NAME OF JOURNAL

World Journal of Methodology

ISSN

ISSN 2222-0682 (online)

LAUNCH DATE

September 26, 2011

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Timotius Ivan Hariyanto

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2222-0682/editorialboard.htm>

PUBLICATION DATE

September 20, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Retrospective Cohort Study

Role of the phase angle in the prognosis of the cirrhotic patient: 15 years of follow-up

Letícia Pereira Pinto, Claudio Augusto Marroni, Juliana Czermainski, Maria Luiza Fernandes Dahlem, Randhall B Carteri, Sabrina Alves Fernandes

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Krygier R, Poland; Tsoulfas G, Greece

Received: July 2, 2023

Peer-review started: July 2, 2023

First decision: July 5, 2023

Revised: July 16, 2023

Accepted: July 25, 2023

Article in press: July 25, 2023

Published online: September 20, 2023



Letícia Pereira Pinto, Claudio Augusto Marroni, Juliana Czermainski, Sabrina Alves Fernandes, Department of Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre 90050-170, Brazil

Maria Luiza Fernandes Dahlem, Department of Veterinary Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre 91540-000, Brazil

Randhall B Carteri, Department of Nutrition, Centro Universitário Metodista IPA, Porto Alegre 90420-060, Brazil

Randhall B Carteri, Department of Nutrition, Centro Universitário Cesuca, Cachoeirinha 94935-630, Brazil

Corresponding author: Sabrina Alves Fernandes, PhD, Research Scientist, Teacher, Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre, Sarmiento Leite 245, Porto Alegre 90050-170, Brazil. sabrinaafernandes@gmail.com

Abstract

BACKGROUND

In 2019, cirrhosis accounted for 2.4% of global deaths. The projection for 2030 is an increase in this index. In recent years, hospitalization costs have escalated by 36% for compensated cirrhosis and 24% for decompensated cirrhosis. Therefore, it is necessary to identify a tool capable of predicting the mortality of these patients according to their clinical condition and consequently extending their survival time. Different studies have shown that the phase angle (PA) can be a feasible method in clinical practice, with the potential to guide assertive patient management in the therapeutic of chronic liver disease.

AIM

To evaluate the prognostic role of PA in cirrhotic patients over a 15-year follow-up period.

METHODS

Retrospective cohort study with 129 cirrhotic patients of both sexes over 18 years old. Diagnosis of cirrhosis by liver biopsy. The first year of data collection was 2007, and data regarding outcomes was collected in 2023. Data were gathered from medical records, such as esophageal varices (EV), EV bleeding, ascites,

spontaneous bacterial peritonitis (SBP), encephalopathy, laboratory findings and PA. The cut-off value for the PA was 5.4° , a value described in 2012 by Fernandes *et al* for 129 patients evaluated in this study and the cut-off points for the Brazilian population presented in percentiles (P), as described by Mattiello *et al*. The mortality was assessed using the PA percentile through Kaplan-Meier curves and multivariate binary logistic regression models.

RESULTS

Patients were divided into two groups according to the PA 5.4th (PA $> 5.4^\circ$, $n = 40$; PA $\leq 5.4^\circ$, $n = 89$) PA percentile ($< P50$, $n = 56$; $\geq P50$ $n = 73$). The percentile classification was more accurate in identifying long-term deaths than the 5.4° PA. Patients with $< P50$ had a higher number of relevant complications such as ascites, SBP, liver encephalopathy and HCC. PA is strongly correlated with serum albumin ($P < 0.001$), International Normalized Ratio ($P = 0.01$), total bilirubin ($P = 0.02$) and direct bilirubin ($P = 0.003$). PA is correlated with survival time ($P < 0.001$) and length of stay ($P = 0.02$). Logistic regression analysis shows that an increase of 1° in PA enlarges the cirrhotic patient's chance of survival by 17.7%.

CONCLUSION

PA is a good predictor of morbidity and mortality for cirrhotic patients. The PA by percentile showed greater sensitivity in predicting mortality compared to the cut-off point of 5.4° .

Key Words: Liver cirrhosis; Phase angle; Prognosis; Liver transplantation; Electrical bioimpedance

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Cirrhosis is characterized by the destruction of hepatic cells, resulting in metabolic alterations that compromise the body's homeostasis. This has a detrimental effect on the patient's clinical condition, negatively impacting their prognosis. Identifying a parameter capable of predicting relevant events is essential for a more assertive approach, reducing mortality and promoting higher life quality. This study aimed to assess the prognostic role of Phase Angle (PA) in cirrhotic patients. One hundred and twenty-nine patients were included, concluding that PA is a promising tool in predicting the clinical condition of chronic liver disease.

Citation: Pinto LP, Marroni CA, Czermainski J, Dahlem MLF, Carteri RB, Fernandes SA. Role of the phase angle in the prognosis of the cirrhotic patient: 15 years of follow-up. *World J Methodol* 2023; 13(4): 238-247

URL: <https://www.wjgnet.com/2222-0682/full/v13/i4/238.htm>

DOI: <https://dx.doi.org/10.5662/wjm.v13.i4.238>

INTRODUCTION

In 2019, cirrhosis was associated with 2.4% of global deaths. The main etiology of cirrhosis during that period was hepatitis C virus infection, followed by alcohol-related liver disease. However, with advancements in the management of viral hepatitis and the increase in obesity levels and alcohol consumption, the epidemiology of cirrhosis is changing, leading to a growing number of cases associated with Metabolic Associated Steatotic Liver Disease (MASLD) and alcohol, an epidemiological situation that results in a reduced mortality rate for other etiologies[1]. It is estimated that mortality from advanced chronic liver disease will more than double between 2016 and 2030[2].

Cirrhosis has a peculiar pathophysiological characteristic, an increase in the body's energy demand, which results in increased depletion of muscle and hepatic glycogen, increased degradation and protein needs, increased lipoperoxidation due to oxidative stress, and activation of the pro-inflammatory cascade, favoring disease progression and development of complications[3].

This disruption of body homeostasis in cirrhosis, regardless of etiology, leads to cellular damage in terms of integrity and functionality, resulting from parenchymal rearrangement, which causes vascular alterations, portal hypertension, and hepatocellular dysfunction. This pathophysiological characteristic substantially impacts the prognosis of cirrhotic patients[4].

Systematically monitoring the progression of chronic liver disease is a complex task for many healthcare services, as it has numerous limitations, such as being an invasive and costly method and discrepancies in the collected data among professionals. Therefore, there is an urgent need to explore new tools, such as a temporal prognostic index of chronic liver disease based on the natural history of the disease.

Currently, it is possible to assess cellular structure through phase angle (PA). PA is derived from the relationship between resistance and reactance, reflecting the conductivity of electric current through body cells. The value of PA expressed in degrees, is measured by the bioelectrical impedance analysis device[5].

Several studies refer to PA as a prognostic indicator because it can measure damage to cellular integrity and functionality resulting from diseases, compromised nutritional status, and/or hydration status. Thus, it is widely used as a guiding parameter in managing various diseases[6-10].

Therefore, we conducted a cohort study of cirrhotic patients with different etiologies to capture longitudinal trajectories over 15 years. We analyzed the association between PA and the two main outcomes, death and liver transplantation. Additionally, we evaluated the correlation of PA with laboratory parameters of liver function, survival curves of the study population according to PA values, and associations of PA with the main complications of cirrhosis, such as ascites, encephalopathy, spontaneous bacterial peritonitis (SBP), and bleeding esophageal varices.

This study suggests that the segmented and systematic use of PA in routine evaluation of cirrhotic patients can provide important information about the patient's health condition at the time of assessment, enabling early and effective therapeutic intervention to extend the survival time of cirrhotic patients while improving their quality of life.

MATERIALS AND METHODS

Study population

A retrospective cohort study was conducted, enrolling cirrhotic patients of both sexes, over 18 years old, treated at the gastroenterology clinic of a hospital complex in Porto Alegre, Brazil. The diagnosis of cirrhosis was established through histological analysis of liver biopsy, imaging tests, and biological markers. Patients with intestinal malabsorption, acquired immunodeficiency syndrome, chronic kidney failure, those on enteral diet, upper limb neuromuscular alterations, chronic pancreatitis, chronic diarrhea, and mental and/or cognitive disorders were excluded from the study. For survival analysis, patients who underwent transplantation during the follow-up were included until the moment of transplantation. This study was conducted in accordance with the Helsinki Declaration and was approved by the ethics and research committee of the Federal University of Health Sciences of Porto Alegre, RS, Brazil, under the number 5203619. All participants signed the Informed Consent Form in advance.

Data collection

Data collection in the first year occurred in January 2007, and data regarding the outcomes were gathered in January 2023. Demographic data such as age and sex were collected. The clinical data on patient outcomes included the number of hospitalizations, ascites, paracentesis, encephalopathy, VE, SBP, and hepatocellular carcinoma (HCC). The staging of cirrhosis was assessed through the Child-Pugh and Model for End-Stage Liver Disease (MELD) scores.

The laboratory tests taken into consideration were those performed up to three months before or after the evaluation, which included: Albumin, aspartate aminotransferase (AST or TGO), alanine aminotransferase (ALT or TGP), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP or FA), bilirubin levels, and International Normalized Ratio (INR). The duration of hospitalization was calculated based on the admission date and discharge date.

Phase angle analysis

The PA data was collected using tetrapolar electrical bioimpedance from the Biodynamics 450 brand. For the test, participants were instructed to remove all metal objects that could interfere with the examination. The patients were positioned in a supine position with the palms of their hands facing down and their arms along their bodies; electrodes were placed on the middle finger and wrist of the right hand and the ankle and middle finger of the right foot. The PA was established using the following formula: $PA = \text{tangent arc } (X_c/R) \times 180/\pi$.

The PA was categorized according to two references for analysis of the outcomes of death and transplantation: Fernandes[7], which establishes the cut-off point for PA at 5.4°. Thus, a PA score of 5.4 points indicates a suboptimal outcome for all statistical evaluations of the study. The additional reference used was Mattiello[11], through their epidemiological study, which establishes cut-off points of PA for the Brazilian population by percentiles (p) p5, p25, p50, p75, p95. The PA value by percentile is distributed considering the age and sex of the studied sample. A PA in the range of the p50 represents the average normality; hence, a p below 50 (< P50) represents a poor prognosis.

Statistical analysis

A general description of the data gathered is provided through simple and relative frequencies. Data normality was assessed using the Shapiro-Wilk test, and the data were compared using the student's t-test for independent samples. Pearson's correlation was used to evaluate potential interactions between different variables. Survival analysis was performed using the Kalan-Meier method, using PA values. Binary logistic regression was also performed to assess the predictive potential of specific variables with the patient's outcome. Significant values were considered when $P < 0.05$. All data were analyzed using the statistical program Statistical Package for Social Sciences version 22.0.

RESULTS

The study assessed 129 cirrhotic patients with an average age of 56.32 (SD 56.32 ± 11.25), with a predominance of male sex (56.6%). The prevailing etiology was hepatitis C virus (43.40%). Other patient characteristics included in the study are described in [Table 1](#).

The clinical condition of the patients was determined by the Child-Pugh score, where 65.89% were classified as A, 25.59% as B, and 8.52% as C. The MELD score showed an average score of 10.70 (SD 10.70 ± 4.70).

Table 1 Characterization of the sample, *n* (%)

Variáveis	Total, <i>n</i> = 129
Age (yr), mean ±SD	56.32 ± 11.25
Gender	
Male	73 (56.6)
Female	56 (43.4)
Weight (kg), mean ± SD	74.46 ± 14.69
Height (m), mean ± SD	164.43 ± 8.97
Phase angle, mean ± SD	6.62 ± 2.95
Etiology Cirrhosis	
Alcohol	31 (24)
Autoimmune	5 (3.90)
Nash	5 (3.90)
Others	16 (12.5)
Virus C	56 (43.40)
Virus C+ alcohol	12 (9.30)
Virus B	4 (3.10)
Meld, mean ± SD	10.98 ± 4.69
Classification Child-Turcotte-Pugh	
Child A	85 (65.89)
Child B	33 (25.59)
Child C	11 (8.52)

NASH: Non-alcoholic steatohepatitis

Table 2 Clinical outcomes according to phase angle classifications, *n* (%)

Variable	<i>n</i> = 129	< 5.4, <i>n</i> = 89	> 5.4, <i>n</i> = 40	< 50, <i>n</i> = 56	> 50, <i>n</i> = 73	mean ± SD, PA
Deaths from the 1 st year to the 5 th year (1-60 mo)	41	17 (41.46)	24 (58.53)	22 (53.65)	18 (46.35)	5.81 ± 1.87
Deaths from the 6 th to the 10 th year (61-120 mo)	19	7 (36.84)	12 (63.15)	10 (52.63)	9 (47.36)	6.63 ± 3.21
Deaths from the 11 th to the 15 th year (121-180 mo)	6	1 (16.67)	5 (83.33)	2 (33.34)	4 (66.66)	6.65 ± 1.90
Alive not transplanted	45	6 (13.33)	39 (86.66)	11 (24.44)	34 (75.55)	7.04 ± 3.07
Alive transplanted	10					8.62 ± 5.48
Dead transplanted	8	4 (50)	4 (50)	6 (75)	2 (25)	5.75 ± 1.01
Deaths from the 1 st year to the 5 th year (1-60 mo)	3	1 (33.33)	2 (66.67)	1 (33.33)	2 (66.67)	6.57 ± 1
Deaths from the 6 th to the 10 th year (61-120 mo)	4	2 (50)	2 (50)	4 (100)	-	5.28 ± 0.56
Deaths from the 11 th to the 15 th year (121-180 mo)	1	1 (100)	0	1 (100)	-	5.19 ± 0

Results expressed by mean ± SD, median ± SD or *n* (%).

The mortality rate of the non-transplanted patients (*n* = 111) over the 15-year period showed that 66 died (59.45%), and among these, 41 (62.12%) died within the first to fifth year, 19 (28.78%) from the sixth to the tenth year, and 6 (9.09%) from the eleventh to the fifteenth year. Of the 41 who died in the first five years, 41.46% had a PA < 5.4° and 53.65% had a percentile < P50. Of the 19 who died between the sixth and tenth year, 36.84% had PA < 5.4, and 52.63% had < P50. The 6 patients who died in the last 5 years of the study, 16.66% had PA < 5.4 and 33.33% had < P50 (Table 2).

Table 3 Clinical outcomes according to phase angle classifications, %

Variables	Total, n = 129	< P50, n = 56	> P50, n = 73
Deaths	57.4	71.40	46.60
SPB	18.6	23.2	15
Ascites	57	66.1	50.70
Paracentesis	30.20	32.10	28.80
EV	75	82.10	69.90
Varicose veins bleeding	10	10.71	10.95
Encephalopathy	34.9	46.40	26
HCC	8.50	10.70	6.80

SPB: Spontaneous bacterial peritonitis; EV: Esophageal varices; HCC: Hepatocellular carcinoma.

Table 4 Biomarkers according to percentil classification

Variable	P < 50, n = 56	P > 50, n = 73	P value
GOT (mg/dL) mean ± Dp	128 ± 428	71 ± 47	0.27
GPT (mg/dL) mean ± Dp	79 ± 227	58 ± 42	0.46
GGT (mg/dL) mean ± Dp	102 ± 80	94 ± 103	0.69
ALP (mg/dL) mean ± Dp	117.4 ± 55.1	101.4 ± 54.6	0.13
Albumin (g/dL) mean ± Dp	3.6 ± 1.9	3.9 ± 0.6	0.34
Total Bilirubin (mg/dL) mean ± Dp	2.4 ± 2.6	1.7 ± 1.2	0.02^a
Direct Bilirubin (mg/dL) mean ± SD	1 ± 1.1	0.7 ± 0.5	0.02^a
Indirect bilirubin (mg/dL) mean ± SD	1.3 ± 1.5	0.9 ± 0.9	0.10
Urea (mg/dL) mean ± SD	36 ± 16	36 ± 13	0.79
Creatinine (mg/dL) mean ± SD	1 ± 0.3	1 ± 0.2	0.64
Sodium (mg/dL) mean ± SD	137 ± 4	139 ± 4	0.03^a
Potassium (mg/dL) mean ± SD	4.6 ± 2	4.9 ± 2.7	0.32
INR mean ± SD	1.36 ± 0.38	1.45 ± 0.51	0.02^a

^aT test for independent samples.

GOT: Oxaloacetic Transaminase; GPT: Pyruvic Transaminase; ALP: Alkaline phosphatase; INR: International normalized ratio.

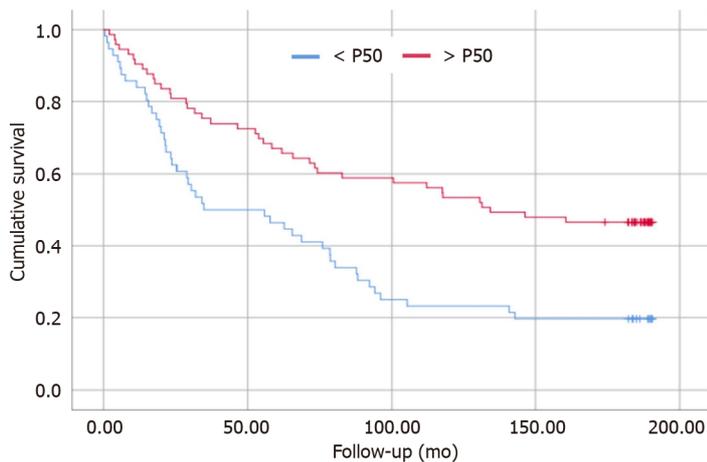
Over the 15 years, 18 patients underwent liver transplantation, and 8 (44.44%) died. Of these, 4 (50%) died in the first six years and the remaining 50% between the seventh and fifteenth year. Of the patients who died between the first and sixth year, 2 (50%) had P50 and a PA 5.40, and those who died between the seventh and fifteenth years, 4 (100%) had P50, and 50% had a PA 5.40.

The average age of the transplanted patients was 51 (SD 51 ± 11) years, 61.11% were male. Among the main causes of transplantation, we cite C virus (27.77%) and C virus + alcohol (16.66%). The leading cause of death of the transplanted patients was post-transplant infection (37.5%). When analyzing the cause of death according to the percentile, infection was the predominant cause (50%) in the < P50 group, while in the >P50 group, the unknown cause and pulmonary cause had the same distribution (50%).

Upon analyzing the clinical outcomes, 57.40% of the patients died due to cirrhosis. Among them, 71.4% had a PA in the P < 50. As for cirrhosis complications, 57% of the patients had ascites, 34% developed encephalopathy, and 75% had esophageal varices (EV), of which 10.9% presented with upper gastrointestinal bleeding (Table 3).

Patients classified between the P25 and P50 had a higher occurrence of EV; however, those classified between the P5 and P25 had a higher occurrence of variceal bleeding as well as encephalopathy.

The serum values of total bilirubin and direct bilirubin were significantly higher in the P < 50 group (P = 0.02) in addition, this same group had significantly lower levels of sodium (P = 0.03) and INR (P = 0.02) as shown in Table 4.



DOI: 10.5662/wjm.v13.i4.238 Copyright ©The Author(s) 2023.

Figure 1 Survival curves.

Upon verifying the relationship between the PA and the duration of hospitalization, the interval in days between hospitalizations, and the survival time, it was observed that the phase angle is significantly correlated with survival time ($R^2 = 0.242$; $P = 0.006$), and the length of hospital stay ($Rho = -0.201$; $P = 0.02$).

The survival curve is a point that deserves attention regarding the PA values reflecting the staging of cirrhosis. Patients with PA < P50 presented higher mortality when compared to patients in the > P50 group (Figure 1). Through logistic regression, for each 1° increase in PA, the patient increases their chance of survival by 17.7%.

DISCUSSION

The natural history of cirrhotic patients indicates an average survival duration of approximately 10 years. However, depending on their clinical conditions, some patients may exhibit distinctive cirrhosis complications that negatively impact morbidity and mortality[12-14].

Early diagnosis or treatment of these complications prolongs survival time, improves the quality of life for cirrhotic patients, and reduces the mortality rate of patients on the waitlist for liver transplantation.

Accordingly, this study evaluated 129 cirrhotic patients over a 15-year follow-up to identify a non-invasive, practical, observer-independent, and easily reproducible parameter capable of predicting cellular impairment in the pathophysiological evolution of cirrhosis.

The demographic characteristics of the population in this study align with the findings of Belarmino's study, which followed 134 cirrhotic patients with an average age of 54.3 (SD 54.3 ± 10.10), predominantly male[4]. Similar demographic findings were noted in Ruiz *et al*'s cohort[15], which assessed 136 cirrhotic patients, again predominantly male, with an average age of 54.5 (SD 54.5 ± 10.0). However, it is noteworthy that the population of this study presented compensated cirrhosis, as opposed to the findings by Belarmino *et al*[4], where only 18% were classified as Child-Pugh A, 55% as B, and 27% as C, and the average MELD score was 14.11 (SD 14.11 ± 4.95). Ruiz *et al*'s study included a homogeneous sample according to the Child-Pugh classification, with 34.1% B, 33.3% C, and a MELD score of 14 (14 ± 6)[15].

Regarding mortality, the increased percentage of deaths is related to a reduction in PA in degrees and percentile. These findings align with Belarmino *et al*[4] study, which identified that patients with PA less than 4.9° , even with compensated cirrhosis, had a higher mortality rate. A similar mortality outcome associated with PA was observed in Saueressig *et al*[16] study, evaluating 97 hospitalized cirrhotic patients with decompensated disease throughout 11.2 mo (2.4-21). However, it is worth highlighting that the same study established 5.52° as the cut-off point for PA, resembling the 5.4° value utilized in this study, but with divergent disease staging characteristics as per the Child-Pugh score, being 9.3% A, 60.8% B, and 29.9% C. This strengthens the hypothesis that PA reflects systemic cellular damage, not solely linked to the parameters used for score calculations.

Regarding liver transplantation, the etiological presence of hepatitis C virus was observed, recalling that data collection began in 2007. Until 2014, hepatitis C cirrhosis was the leading cause of liver transplantation. However, a study conducted between 2014 and 2019, including 51329 patients listed for transplantation, demonstrated a change in this scenario due to an increased incidence of MASLD and alcoholic cirrhosis, justified by rising obesity levels and an increase in alcoholic individuals[17].

Serrano *et al*[18] study, evaluating the outcome of 15998 liver transplants over 10 years, sustains the findings of this study, showing an exponential increase in the mortality rate. On the other hand, the authors observed a difference in survival between men and women, as in the first year, male mortality was higher, which did not occur in subsequent years. This difference in findings between the two studies can be justified by the size of the population studied by Serrano *et al*[18].

Nitski *et al*[19] evaluated 42146 Liver transplant recipients from the Scientific Registry of Transplant Recipients in the US (UHN) and data from the University Health Network (UHN) in Canada, with average follow-ups of 8 and 5 years, respectively, and found that among the leading causes of death in post-liver transplant patients were various types of cancer, infection, organ rejection, and cardiovascular causes, including stroke. These findings align with the results found in this study, which shows a predominance of deaths due to infection followed by HCC and stroke. Patients who died due to infection had $< P50$, demonstrating the potential of PA as a predictive value of cellular impairment related to the inflammatory process[20,21].

Ascites, encephalopathy, and EV are commonly observed complications in the cirrhosis picture. Román *et al*[22], evaluating 100 cirrhotic patients, described that 63% of these had ascites, 12% had encephalopathy, and 31% had EV, unlike the findings of this study, which showed a prevalence of encephalopathy and EV. The difference in disease staging could explain the difference between the studies, as in Román *et al*'s study, 81% of patients were classified as Child-Pugh A[23].

Shi *et al*[24] evaluated 248 cirrhotic patients over 4 years, with the variables analyzed including serum levels of AST, GGT, AP, bilirubin, albumin, and PA. The authors presented a statistically significant correlation of patients with $PA < 5.1^\circ$ (the cut-off point for this patient sample) with increased levels of albumin, total and direct bilirubin, which corroborates this study.

Hospitalization costs for cirrhotic patients grew by 30.2% from 2008 to 2014. Concurrently, there was a 36% increase in hospitalizations of compensated cirrhotic patients and a 24% gain in those of decompensated patients. Hospitalizations of patients with decompensated cirrhosis represented 58.6% of the total hospitalizations of cirrhotic patients in 2014. The main operators of rising costs are the costlier procedures, escalating from 15% to 152%, and the presence of clinical complications[25].

Román *et al*[22] observed that PA is also related to the occurrence of clinically relevant events. The same was observed in this study, where a significant correlation was found between PA, the number of hospitalizations ($P = 0.01$), length of hospital stay ($P = 0.003$), and mortality ($P = 0.001$).

The survival curve presented by various studies[7,26-29] evaluating PA in cirrhotic patients reinforces the results found in this study, demonstrating that a reduction in PA, regardless of the cut-off point, is associated with a growth in morbidity and mortality of cirrhotic patients.

Among the study's limitations, we mention the manual recording of collected data in the patient's medical record, which makes detailing some information impracticable, such as the degree of cirrhosis complications. However, the outcome of the 129 patients included in the study was described.

CONCLUSION

This study is a pioneer on PA as a predictor of mortality in cirrhotic patients, with PA values per percentile for the Brazilian population. The PA by percentile showed greater sensitivity in predicting mortality compared to the cut-off point of 5.4° .

The PA, measured through electrical bioimpedance, can be measured in a segmented way, where the patient can be evaluated daily. In more specific cases, such as in the case of ascites, the measurement of the PA can be performed before and after the paracentesis, informing the cellular condition after a procedure. Thus, the PA becomes a guiding tool in the clinical management of cirrhotic patients by significantly reducing the number of events due to complications characteristic of chronic liver disease. The use of PA can bring as positive outcomes: a lower number and length of hospitalizations, improved quality of life, better results in liver transplantation and, consequently, increased survival time.

ARTICLE HIGHLIGHTS

Research background

The number of new cases of cirrhotic patients is growing worldwide and, as a consequence, an increase in the demand for specialized care to treat the disease *per se* and the complications inherent in cirrhosis, in addition to the increase in patients on the waiting list for orthotopic transplantation of liver. Given this scenario, it is necessary to identify a tool to predict the mortality of these patients linked to their clinical condition. Within this perspective, the phase angle (PA) becomes a good alternative because it is a viable method in clinical practice, with the potential to guide the clinical management of the patient and extend their survival time and better quality of life.

Research motivation

Identifying a tool capable of predicting mortality and severity of chronic liver disease in real time as a clinical practice brings numerous benefits to this population and to the professionals who treat them.

Research objectives

To the best of our knowledge, no study has evaluated the role of PA as a predictor of mortality in cirrhotic patients with a 15-year follow-up.

Research methods

Retrospective cohort study with 129 cirrhotic patients of both genders aged over 18 years. Diagnosis of cirrhosis by liver biopsy. The cut-off value for the PA was 5.4°, a value described in 2012 by Fernandes *et al* for 129 patients evaluated in this study and the cut-off points for the Brazilian population presented in percentiles (P), as described by Mattiello *et al.* Mortality was assessed using the PA percentile using Kaplan-Meier curves and multivariate binary logistic regression models.

Research results

The percentile ranking was more accurate in identifying long-term deaths than the 5.4th PA. Patients with < P50 had a higher number of relevant complications, such as ascites, SBP, liver encephalopathy and HCC. PA is strongly correlated with serum albumin ($P < 0.001$), INR ($P = 0.01$), total bilirubin ($P = 0.02$) and direct bilirubin ($p = 0.003$). PA is correlated with survival time ($P < 0.001$) and length of stay ($P = 0.02$). Logistic regression analysis shows that a 1° increase in PA increases the chance of survival of cirrhotic patients by 17.7%.

Research conclusions

PA is a good predictor of morbidity and mortality for cirrhotic patients.

Research perspectives

Identifying clinical factors that enhance a poor prognosis for cirrhotic patients, such as ascites, encephalopathy, length of stay, is relevant. With this information, it is possible to act early in the clinical management of these patients and increase the effectiveness of the therapeutic response, with consequent improvement in the prognosis and quality of life of this population.

FOOTNOTES

Author contributions: Pinto LP contributed to the methodological development and material support, collected data, interpreted results, conducted data analysis, wrote and revised the manuscript; Marroni AC contributed to the conception and critical review of the manuscript; Czermainski J collected data and interpreted the results; Dahlem MLF contributed to the methodological development and material support; Carteri R conducted data analysis and interpreted the results; Fernandes SA designed the research project, collaborated in writing, and critically reviewed the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: This study was conducted in accordance with the Helsinki Declaration and was approved by the ethics and research committee of the Federal University of Health Sciences of Porto Alegre (UFCSPA), RS, Brazil, under the number 5203619. All participants signed the Informed Consent Form (TCLE) in advance.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: There is no conflict of interest for any of the researchers.

Data sharing statement: No additional data is available for sharing.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Brazil

ORCID number: Leticia Pereira Pinto 0000-0001-8543-1587; Claudio Augusto Marroni 0000-0002-1718-6548; Juliana Czermainski 0000-0002-4628-2467; Maria Luiza Fernandes Dahlem 0009-0009-6088-0074; Randhall B Carteri 0000-0003-4124-9470; Sabrina Alves Fernandes 0000-0001-8504-603X.

S-Editor: Liu JH

L-Editor: A

P-Editor: Liu JH

REFERENCES

- 1 Huang DQ, Terrault NA, Tacke F, Glud LL, Arrese M, Bugianesi E, Loomba R. Global epidemiology of cirrhosis - aetiology, trends and

- predictions. *Nat Rev Gastroenterol Hepatol* 2023; **20**: 388-398 [PMID: 36977794 DOI: 10.1038/s41575-023-00759-2]
- 2 **Estes C**, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, Colombo M, Craxi A, Crespo J, Day CP, Eguchi Y, Geier A, Kondili LA, Kroy DC, Lazarus JV, Loomba R, Manns MP, Marchesini G, Nakajima A, Negro F, Petta S, Ratziu V, Romero-Gomez M, Sanyal A, Schattenberg JM, Tacke F, Tanaka J, Trautwein C, Wei L, Zeuzem S, Razavi H. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol* 2018; **69**: 896-904 [PMID: 29886156 DOI: 10.1016/j.jhep.2018.05.036]
 - 3 **Bittencourt PL**, Zollinger CC. Manual de cuidados intensivos em hepatologia. Online 2017. [acesso em: maio de 2012]; Available from: sbhepatologia.org.br/wpcontent/uploads/2017/10/Manual-de-Cuidados-Intensivos-em-Hepatologia-1.pdf
 - 4 **Belarmino G**, Gonzalez MC, Torrinhas RS, Sala P, Andraus W, D'Albuquerque LA, Pereira RM, Caparbo VF, Ravacci GR, Damiani L, Heymsfield SB, Waitzberg DL. Phase angle obtained by bioelectrical impedance analysis independently predicts mortality in patients with cirrhosis. *World J Hepatol* 2017; **9**: 401-408 [PMID: 28321276 DOI: 10.4254/wjh.v9.i7.401]
 - 5 **Ramos L**, Eickemberg M, Moreira P, de Oliveira CC. Bioimpedância elétrica. 2012 [DOI: 10.7476/9788523218744.0009]
 - 6 **Nunes G**, Santos CA, Barosa R, Fonseca C, Barata AT, Fonseca J. Outcome and nutritional assessment of chronic liver disease patients using anthropometry and subjective global assessment. *Arq Gastroenterol* 2017; **54**: 225-231 [PMID: 28723979 DOI: 10.1590/s0004-2803.201700000-28]
 - 7 **Fernandes SA**, Bassani L, Nunes FF, Aydos ME, Alves AV, Marroni CA. Nutritional assessment in patients with cirrhosis. *Arq Gastroenterol* 2012; **49**: 19-27 [PMID: 22481682 DOI: 10.1590/S0004-28032012000100005]
 - 8 **Fernandes SA**. O ângulo de Fase como marcador prognóstico associado ao estado nutricional do cirrótico e à gravidade da doença: do modelo clínico ao experimental. Porto Alegre. Dissertação [Mestrado em Medicina: Hepatologia] – Universidade Federal de Ciências da Saúde de Porto Alegre; 2013
 - 9 **Marroni CA**, Miranda D, Boemeke L, Fernandes SA. Phase angle bioelectrical impedance analysis (BIA) as a biomarker tool for liver disease. Biomarkers in Liver Disease: Biomarkers in Disease: Methods, Discoveries and Applications. Berlin: Springer Science, 2017; 735-751. Available from: https://link.springer.com/referenceworkentry/10.1007/978-94-007-7742-2_43-1
 - 10 **Norman K**, Stobäus N, Pirllich M, Bopsy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. *Clin Nutr* 2012; **31**: 854-861 [PMID: 22698802 DOI: 10.1016/j.clnu.2012.05.008]
 - 11 **Mattiello R**, Mundstock E, Ziegelmann PK. Brazilian Reference Percentiles for Bioimpedance Phase Angle of Healthy Individuals. *Front Nutr* 2022; **9**: 912840 [PMID: 35873414 DOI: 10.3389/fnut.2022.912840]
 - 12 **D'Amico G**, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; **44**: 217-231 [PMID: 16298014 DOI: 10.1016/j.jhep.2005.10.013]
 - 13 **Tsochatzis EA**, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014; **383**: 1749-1761 [PMID: 24480518 DOI: 10.1016/S0140-6736(14)60121-5]
 - 14 **Ginès P**, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet* 2021; **398**: 1359-1376 [PMID: 34543610 DOI: 10.1016/S0140-6736(21)01374-X]
 - 15 **Ruiz-Margáin A**, Xie JJ, Román-Calleja BM, Pauly M, White MG, Chapa-Ibargüengoitia M, Campos-Murguía A, González-Regueiro JA, Macías-Rodríguez RU, Duarte-Rojo A. Phase Angle From Bioelectrical Impedance for the Assessment of Sarcopenia in Cirrhosis With or Without Ascites. *Clin Gastroenterol Hepatol* 2021; **19**: 1941-1949.e2 [PMID: 32890753 DOI: 10.1016/j.cgh.2020.08.066]
 - 16 **Saueressig C**, Glasenapp JH, Luft VC, Alves FD, Ferreira PK, Hammes TO, Dall'Alba V. Phase Angle Is an Independent Predictor of 6-Month Mortality in Patients With Decompensated Cirrhosis: A Prospective Cohort Study. *Nutr Clin Pract* 2020; **35**: 1061-1069 [PMID: 33058222 DOI: 10.1002/ncp.10584]
 - 17 **Wong RJ**, Singal AK. Trends in Liver Disease Etiology Among Adults Awaiting Liver Transplantation in the United States, 2014-2019. *JAMA Netw Open* 2020; **3**: e1920294 [PMID: 32022875 DOI: 10.1001/jamanetworkopen.2019.20294]
 - 18 **Serrano MT**, Sabroso S, Esteban LM, Berenguer M, Fondevila C, Lorente S, Cortés L, Sanchez-Antolin G, Nuño J, De la Rosa G, Salcedo M. Mortality and Causes of Death After Liver Transplantation: Analysis of Sex Differences in a Large Nationwide Cohort. *Transpl Int* 2022; **35**: 10263 [PMID: 35615539 DOI: 10.3389/ti.2022.10263]
 - 19 **Nitski O**, Azhie A, Qazi-Arisar FA, Wang X, Ma S, Lilly L, Watt KD, Levitsky J, Asrani SK, Lee DS, Rubin BB, Bhat M, Wang B. Long-term mortality risk stratification of liver transplant recipients: real-time application of deep learning algorithms on longitudinal data. *Lancet Digit Health* 2021; **3**: e295-e305 [PMID: 33858815 DOI: 10.1016/S2589-7500(21)00040-6]
 - 20 **Lee GR**, Kim EY. Usefulness of phase angle on bioelectrical impedance analysis as a surveillance tool for postoperative infection in critically ill patients. *Front Med (Lausanne)* 2023; **10**: 1111727 [PMID: 36910475 DOI: 10.3389/fmed.2023.1111727]
 - 21 **Ceolin J**, de Borja EL, Mundstock E, de Oliveira JR, Mattiello R, Bodanese LC. Phase angle of bioimpedance as a marker of inflammation in cardiovascular diseases: A systematic review. *Nutrition* 2023; **112**: 112064 [PMID: 37263162 DOI: 10.1016/j.nut.2023.112064]
 - 22 **Román E**, Poca M, Amorós-Figueras G, Rosell-Ferrer J, Gely C, Nieto JC, Vidal S, Urgell E, Ferrero-Gregori A, Alvarado-Tapias E, Cuyàs B, Hernández E, Santemas R, Guarner C, Escorsell À, Soriano G. Phase angle by electrical bioimpedance is a predictive factor of hospitalisation, falls and mortality in patients with cirrhosis. *Sci Rep* 2021; **11**: 20415 [PMID: 34650096 DOI: 10.1038/s41598-021-99199-8]
 - 23 **Liu YB**, Chen MK. Epidemiology of liver cirrhosis and associated complications: Current knowledge and future directions. *World J Gastroenterol* 2022; **28**: 5910-5930 [PMID: 36405106 DOI: 10.3748/wjg.v28.i41.5910]
 - 24 **Shi JY**, Yang G, Liu B, Shang X, Cui GZ, Huang JX, Wang WT, Chen KY, Wang NY. Low Phase Angle Predicts Poor Survival in Patients with Hepatocellular Carcinoma: A Retrospective Study. *Journal of Nutritional Oncology* 2022; **7**: 75-84 [DOI: 10.34175/jno202202003]
 - 25 **Desai AP**, Mohan P, Nokes B, Sheth D, Knapp S, Boustani M, Chalasani N, Fallon MB, Calhoun EA. Increasing Economic Burden in Hospitalized Patients With Cirrhosis: Analysis of a National Database. *Clin Transl Gastroenterol* 2019; **10**: e00062 [PMID: 31343469 DOI: 10.14309/ctg.000000000000062]
 - 26 **Ruiz-Margáin A**, Macías-Rodríguez RU, Duarte-Rojo A, Ríos-Torres SL, Espinosa-Cuevas Á, Torre A. Malnutrition assessed through phase angle and its relation to prognosis in patients with compensated liver cirrhosis: a prospective cohort study. *Dig Liver Dis* 2015; **47**: 309-314 [PMID: 25618555 DOI: 10.1016/j.dld.2014.12.015]
 - 27 **Selberg O**, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. *Eur J Appl Physiol* 2002; **86**: 509-516 [PMID: 11944099 DOI: 10.1007/s00421-001-0570-4]
 - 28 **Peres WA**, Lento DF, Baluz K, Ramalho A. Phase angle as a nutritional evaluation tool in all stages of chronic liver disease. *Nutr Hosp* 2012; **27**: 2072-2078 [PMID: 23588459 DOI: 10.3305/nh.2012.6.6015]

- 29 **Bosy-Westphal A**, Danielzik S, Dörhöfer RP, Later W, Wiese S, Müller MJ. Phase angle from bioelectrical impedance analysis: population reference values by age, sex, and body mass index. *JPEN J Parenter Enteral Nutr* 2006; **30**: 309-316 [PMID: 16804128 DOI: 10.1177/0148607106030004309]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

