Daniela Cortes ORCID iD: 0000-0001-9854-2761

Ramona Boulhosa ORCID iD: 0000-0001-7590-5793
CARLA CUNHA ORCID iD: 0000-0002-9644-7194
Allain Bueno ORCID iD: 0000-0002-9456-8558

Handgrip strength is associated with 12 months survival in male patients suffering with advanced chronic liver disease

Daniela Moreno Côrtes[1], Ramona Souza da Silva Baqueiro Boulhosa[1], Cláudio Luiz da Silva Lima Paz[2], Carla de Magalhães Cunha[3], Lucivalda Pereira Magalhães de Oliveira[3], André Castro Lyra[4], Allain Amador Bueno[5], Rosângela Passos de Jesus[3]

1. Food, Nutrition and Health Post-Graduation Program, Federal University of Bahia, Salvador, Bahia 40110-150, Brazil
2. Bahia Social College, Salvador, Bahia 40.170-010, Brazil.
3. Science Nutrition Department, Federal University of Bahia, Salvador, Bahia 40110-150, Brazil
4. Department of Gastroenterology, Federal University of Bahia, Salvador, Bahia, 40110-060, Brazil
5. College of Health, Life and Environmental Sciences, University of Worcester, Worcester WR2 6AJ, United Kingdom

Corresponding Author

Daniela M Côrtes. Food, Nutrition and Health Post-Graduation Program, Federal University of Bahia, Salvador, Bahia 40110-150, Brazil. Phone number: +5571996525004. Email: danielamorenno@gmail.com

Daniela Moreno Côrtes

Food, Nutrition and Health Post-Graduation Program, Federal University of Bahia, Salvador, Bahia 40110-150, Brazil

Phone number: +5571996525004 Email: danielamorenno@gmail.com

Keypoints

1. Strength measurement is an indicator of nutritional status that is not compromised by the presence of edema and ascites and, therefore, has an advantage over methods traditionally used in clinical practice for ACLD patients;

2. However, to date very few studies have presented cutoff values for ACLD patients. Furthermore, studies that have accounted for variables that directly

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jhn.13160.

influence muscle strength, including age group and the various levels of severity of liver disease, are scarce;

3. As dynamometry is a low-cost method and easily reproducible in clinical practice, HGS can be effectively applied for inpatient and outpatient nutritional care. HGS cutoff values may be used to plan a more tailored nutritional therapy and, most importantly, for the early detection of individuals at greater risk of negative outcomes in ACLD.

4. The results of the present study show that reduced HGS was associated with increased mortality and reduced survival in ACLD male patients.

5. A multicentre study which presents HGS cutoff accurate enough to predict mortality in larger populations of ACLD adult and elderly patients of both sexes will bring certainty as to the applicability of our results to larger settings.

Affiliation, biography and contribution of authors:

1. Daniela Moreno Côrtes

Food, Nutrition and Health Post-Graduation Program, Federal University of Bahia, Salvador, Bahia 40110-150, Brazil

Phone number: +5571996525004 Email: danielamorenno@gmail.com

Master in food, nutrition and health, member of the Nucleus of Research in Nutrition and Chronic Diseases and active collaborator in research and scientific publications in the area of nutrition and hepatology.

Cortes DM was responsible for the conception, design and coordination of the study; acquisition, analysis, and interpretation and discussion of data. Cortes DM performed statistical analyses and drafted the manuscript.

2. Ramona S S B Boulhosa

Food, Nutrition and Health Post-Graduation Program, Federal University of Bahia, Salvador, Bahia 40110-150, Brazil.

Phone number: +5571999674891 Email: ramonabaqueiro@hotmail.com

PhD in Food, Nutrition and Health; expertise in nutritional assessment and nutritional care for patients with chronic liver disease.

Boulhosa RSSB was responsible for the conception, acquisition, analysis, and interpretation and discussion of data. Boulhosa RSSB performed statistical analyses and drafted the manuscript.

3. Cláudio L S L Paz

Bahia Social College, Salvador, Bahia 40.170-010, Brazil.

Phone number: +5571981841069 E-mail: claudio.paz@outlook.com.br

Researcher in the area of Health Technology Assessments with emphasis on Evidence-Based Health, biostatistics and Systematic Reviews and Meta-analyses.

Paz CLSL was responsible for statistical analyses.

4. Carla de Magalhães Cunha

Science Nutrition Department, Federal University of Bahia, Salvador, Bahia 40110-150, Brazil

Phone number: +5571999698689 Email: carlamagalhaesc@gmail.com

Biography

Nutritionist and Master from the Federal University of Bahia, member of the Nucleus of Research in Nutrition and Chronic Diseases and actively collaborates in relevant scientific publications on the subject

Abstract

Advanced chronic liver disease (ACLD) patients are usually malnourished, and both conditions in combination increase the likelihood of unfavourable clinical outcomes. Handgrip strength (HGS) has been suggested as a relevant parameter for nutritional assessment and predictor of adverse clinical outcomes in ACLD. However, the HGS cutoff values for ACLD patients have not yet been reliably established. The aims of this study were to preliminarily identify HGS reference values in a sample population of ACLD male patients, and to assess their association with survival over a 12-month follow-up period. This was a prospective observational study with preliminary analysis of outpatients and inpatients. One hundred eighty-five male patients with a medical diagnosis of ACLD met the inclusion criteria and were invited to participate in the study. The physiological variation in muscle strength related to the age of the individuals included in the study was considered to obtain cutoff values. After categorising HGS by age group (adults: 18 to 60 years; elderly: ≥ 60 years), the reference values obtained were 32.5 kg for adults and 16.5 kg for the elderly. During the 12-month follow-up, 20.5% of the patients died, and 76.3% of those had been identified with reduced HGS. Patients with adequate HGS showed significantly higher 12-month survival compared to those with reduced HGS within the same period. Our findings show that HGS is an important predictive parameter for clinical and nutritional follow-up in ACLD male patients.

Keywords: Handgrip strength; cutoff values; advanced chronic liver disease; 12 months survival; Child-Pugh; Subjective Global Assessment

Introduction

Advanced chronic liver disease (ACLD) is the final stage of evolution of chronic liver diseases and has major clinical relevance due to the complexity of its pathophysiological mechanisms, multiple aetiological factors and high mortality rate. ACLD is characterised by impairment of the lobular architecture of the liver, histologically defined by the presence of diffuse fibrosis and the development of regenerative nodules, which functionally affect the hepatic parenchyma [1, 2].

Hypermetabolism, inflammatory and neuroendocrine disturbances triggered by ACLD can induce ascites, early satiety, increased proteolysis and reduced protein synthesis, which in combination can further exacerbate malnutrition. Malnutrition in ACLD patients may be associated with reduced muscle strength (dynapenia), and reduced muscle mass and function (sarcopenia). Such metabolic and physiological manifestations significantly increase mortality risk, reduce quality of life, impair mobility and worsens the ACLD prognosis [3, 4, 5, 6].

Long-established associations between malnutrition and unfavourable clinical outcomes in ACLD confirm the need for reproducible, reliable and affordable methods for nutritional assessment of ACLD patients. The identification of suitable biomarkers in ACLD would facilitate early diagnosis and enable targeted and more effective clinical and nutritional interventions for the ACLD population [2, 7].

Strength measurement is an indicator of nutritional status that is not compromised by the presence of oedema and ascites and, therefore, has an advantage over methods traditionally used in clinical practice, such as body weight and Body Mass Index (BMI) (8). Clinical and epidemiological studies have used dynamometry to quantify handgrip strength (HGS), which is representative of total muscle strength. Handgrip dynamometry is a non-invasive, practical and quick method that does not accrue additional costs and that can be performed at the bedside, being a valuable tool for the nutritional assessment of bedridden patients [9, 10].

Due to the many advantages of handgrip dynamometry in clinical practice, muscle strength has been identified as an important prognostic tool in several clinical conditions, for example in chronic kidney disease and for individuals undergoing cardiac surgery [11, 12]. In ACLD patients, reduced HGS has been suggested as predictor of adverse clinical outcomes [5, 6]. However, to date very few studies have presented cutoff values for ACLD patients. Furthermore, studies that have accounted for variables that directly influence muscle strength, including age group and the various levels of severity of liver disease, are scarce.

The determination and validation of HGS cutoff values that have a good predictive capacity for adverse outcomes in ACLD may facilitate a more accurate identification of disease status and progression according to the clinical and epidemiological characteristics of that population, enabling earlier intervention. The aim of the present study was to preliminarily identify HGS reference values in male ACLD patients, and to subsequently investigate their association with survival during a 12-month follow-up period.

Method

Sample population and study design

This was a prospective observational pilot study carried out at the Department of Gastroenterology and Hepatology at the Hospital Universitário Professor Edgard Santos, Bahia Federal University, Salvador, Brazil. The participants in this study were patients monitored on an outpatient basis or hospitalised at the Complexo Hospitalar Universitário, from April 2018 to November 2020. This study received full ethical approval by the Research Ethics Committee of university hospital, under registration number 3.380.156. All patients who met the inclusion criteria and agreed to voluntarily participate in the study signed the Free and Informed Consent Form (FICF).

Male patients aged 18 years or older with a clinical or histological diagnosis of ACLD were included. All levels of ACLD severity were included based on the Child-Pugh classification. Patients who presented chronic comorbidities including cardiovascular disease, HIV-AIDS, active pulmonary tuberculosis, rheumatological diseases and hepatocellular carcinoma were not included in the study. The absence of updated clinical information, including updated biochemical parameters, as well as loss of contact with the patients during follow-up, were the exclusion criteria adopted for this study.

Data collection procedure

During the study period, 200 male patients who agreed to participate in the study were interviewed and evaluated by a trained nutritionist member of the research team. Demographic data were obtained through a face-to-face appointment. Hospitalised patients were assessed within the first 48 hours after admission, and those treated in an outpatient setting were assessed at the first nutritional consultation. All patients were followed up for 12 months to assess survival, which in this study was considered the main outcome variable. Based on the exclusion criteria set above, 15 patients from the 200 initially recruited were excluded.

Clinical data

Clinical data, the aetiology of chronic liver disease, and biochemical parameters were obtained through face-to-face appointments and handling of medical records available in the health information system of the university teaching hospital.

The ACLD severity level was obtained through the Child-Pugh classification, which categorises liver dysfunction into mild, moderate and severe, through scores A, B and C, respectively [(13)]. Patients with Child-Pugh classification in category A were evaluated separately as this category covers liver disease in the compensated phase. Patients with Child-Pugh classification in categories B and C were analysed together as both categories cover the ACLD in decompensation phase.

The Model for End-Stage Liver Disease Sodium (MELD-Na) was also deployed to assess the level of liver disease severity through a specialised application. The MELD-Na severity indicator considers the plasma values of albumin, total bilirubin, urea, creatinine, international normalised ratio (INR) and sodium.

For the purpose of study analysis, the MELD-Na value recorded at the beginning of the follow-up was used, considering that patients with a MELD-Na value above 15 were at higher risk of death (13). Although the Brazilian guidelines still adopt the traditional MELD score to prioritise allocation in the liver transplant waiting list [(13)], MELD-Na was used in this study as it is used globally due to the incorporation of sodium to assess hyponatremia [14]. All patients were also clinically assessed at baseline and at subsequent visits to identify the presence and level of ascites and hepatic encephalopathy.

Nutritional assessment

The patients' body weight was obtained using a digital scale model SECA 803 with 150 kg capacity and 100 g accuracy. For patients with peripheral oedema and ascites, dry weight was calculated reducing 5, 10, or 15% of current weight if ascites was considered mild, moderate, or severe, respectively. In addition, we carried out a further 5% reduction in body weight in patients who also showed signs of fluid retention in the lower limbs, as suggested by Merli *et al* [7].

Body Mass Index (BMI) was calculated from the ratio between the current weight or dry weight (Kg) / height (m^2) and the reference values proposed by the World Health Organization were adopted [15].

Nutritional status screening was performed using the Subjective Global Assessment (SGA) proposed by Detsky *et al* (1987), which considers the patient's clinical history and physical examination. Based on the joint analysis of clinical history and physical examination, and the parameters obtained by the SGA, the patients were classified as: (A) well-nourished; (B) at risk or moderately malnourished; (C) severely malnourished. Categories B and C were grouped together for statistical analysis [17].

Handgrip strength

HGS was assessed using a Jamar® hydraulic dynamometer with a 0-100 kg graduation scale, following the technique described by Hillman *et al*. (2005). Briefly, the patient remained in a seated position, with legs positioned vertically and feet flat on the floor, forming 90° angles at the hip, knee, and ankle joints. The test arm – the dominant arm – was kept relaxed, rested on the thigh and held close to the body, with the elbow flexed at 90°, with the palm of the hand facing the body and thumb pointing upwards. Patients were asked to perform maximum compression of the dynamometer for 3 seconds. The measurements were repeated 3 consecutive times, with a break of 30 seconds in between measurements. The largest of the three measurements was noted. When the measurement was not possible due to incapacity of the hands, or disabling diseases such as arthritis and sequelae of stroke, the measurement was not performed and the patient was excluded from the study sample.

The physiological variation of muscle strength related to the age of the individuals included in the study was considered for the determination of reference values. For the purpose of statistical analyses, the participants were grouped into two subgroups based on their age: adults (18 to 59 years) or elderly (60 years or older).

We are aware that many previously published studies refer to elderly as people aged 65 years or older, but the current population in Brazil is in average much younger as compared to other nations, particularly the more economically developed ones.

Survival at 12 months

Survival information after the face-to-face assessment in the nutrition clinic or hospital was obtained through periodical monitoring for 12 months. Clinical records available in the hospital integrated digital information system, as well as the official national death registration system, were used as monitoring tools. In the absence of information in those two databases for a period longer than six months, the research team contacted the patients or their families to assess their clinical condition or identify possible death. Death from any cause was considered for inclusion in the analyses.

Statistical analysis

Data distribution normality was examined through visual analysis of the normal curve and confirmed through the Shapiro-Wilk and Kolmogorov-Smirnov tests. For the descriptive analysis, the variables were described through frequencies, measures of central tendency and their dispersions. Continuous data with normal distribution were described as mean and standard deviation, while non-parametric data were described as median and interquartile ranges. For the parametric variables, the unpaired Student's T test was used to compare the means between the groups of non-survivors within 12 months, and the Mann-Whitney test was used for non-normal data. For qualitative variables, results were expressed as percentages and the Chi-square test was used to assess associations.

The HGS reference values for each group (adult and elderly), as well as the sensitivity and specificity of those values, were performed using the Receiver Operating Characteristic (ROC) Curve. Two curves were produced, one for each age group. To calculate the efficiency of each curve and help define the cutoff value, the highest value of the Youden index (Sensitivity + Specificity - 1) was used [19].

The Diagnostic Odds Ratio (DOR) was calculated according to the formula DOR = (sensitivity/(1 – sensitivity)) / ((1 – specificity) / specificity). A higher DOR value is indicative of better test performance. A value of one indicates that the criterion does not discriminate between patients who died and those who did not [19].

The probabilities of survival over the 12 months follow-up in both groups were estimated using the Kaplan-Meier method and compared using the log-rank test. Additionally, the suggested HGS cutoff point for predicting survival was calculated in univariate and multivariate Cox regression models of mortality adjusted for variables with a potential impact on the severity and prognosis of ACLD, including Child-Pugh and MELD-Na scores.

All statistical analyses were performed using SPSS 22 software (SPSS, Chicago, IL, USA). Statistically significant differences were defined where $p \leq 0.05$.

Results

Based on the previously defined inclusion and exclusion criteria, 185 male patients from the 200 initially included in the study remained in the final analysis. Most of the patients included were adults, 61.6% of the sample population (n=114), with the remaining 38.4% (n=71) in the elderly group. No differences in BMI across groups were identified (Table 1).

HGS was significantly reduced in both adult ($p = 0.048$) and elderly ($p = 0.031$) groups in the sample population that did not survive the 12-months follow-up. MELD-Na was significantly elevated in the elderly group that did not survive ($p = 0.024$) as compared to elderly survivors, but statistically similar between both adult groups ($p = 0.256$). MELD was significantly elevated in both groups (adult $p < 0.000$, elderly $p = 0.041$) of non-survivors (Table 1).

The proportion of participants with an SGA of moderately or severely malnourished, and those diagnosed with a Child-Pugh B or C, were significantly higher in both groups that did not survive the 12-months follow up. The ACLD aetiology was dissimilar between both groups, with alcoholic aetiology being significantly more prevalent in the adult group ($p = 0.020$), but no statistically significant differences were observed in the aetiology within the elderly group (Table 1).

In our study, the HGS reference cutoff value that more accurately predicted death as outcome at 12 months in adults was 32.5 kg (Fig. 1A, $p = 0.05$). Considering the Diagnostic Odds Ratio (DOR), adults with a HGS below the reference cutoff value were 7 times more likely to die during the follow-up period than individuals with higher HGS. In the elderly group, HGS less than or equal to 16.5 kg (Fig. 1B, $p = 0.043$) was able to predict mortality, with 4 times more chance of elderly patients having died within 12 months based on DOR. The results of the ROC curves for each age group and the application of the Youden (J) index criterion for each age group can be seen in Figures 1A and 1B.

After obtaining the HGS and its categorisation, Cox regression was performed (Table 2). It was observed that reduced HGS was significantly associated with higher mortality (HR: 3.515; 95%CI: 1.663 – 7.432). This association was maintained even after adjustments that considered the level of liver disease decompensation (Child-Pugh B+C) and the mean MELD-Na score (Table 2).

Figure 2 shows the total survival analysis at 12 months observing the adequacy or inadequacy of the established HGS reference values. In general, it can be observed that patients with adequate HGS had a higher 12-month survival compared to those whose HGS was reduced within the same period ($p < 0.000$). Out of all patients who did not survive the 12 months period, 76.31% (n=38) were identified with reduced HGS, regardless of age (data not shown).

Discussion

Decreased HGS is often detected in ACLD patients. The precise mechanism of HGS reduction in that population remains poorly understood as several metabolic and hormonal disorders inherent to the pathophysiology of the disease may come into play. In addition, dietary restrictions related to complications as the disease progresses, such as ascites, oesophageal varices and hepatic encephalopathy, can reduce food intake and consequently induce muscle catabolism. Increased proteolysis and reduced protein synthesis may contribute to the development and progression of malnutrition and sarcopenia. However, as much as nutritional deficits are related to low muscle strength or dynapenia, they are not the only causes of HGS impairment in ACLD patients. Under physiological conditions, ammonia is detoxified by the urea cycle in the liver parenchyma, more specifically in hepatocytes. On the other hand, in ACLD patients, hyperammonaemia induced by hepatocellular dysfunction may contribute to increased concentrations of myostatin, a cytokine related to strong suppression of protein synthesis and muscle cell proliferation [(21)].

Following the lines of previous studies, our results show that HGS was reduced in adults and the elderly that did not survive the 12-months follow up. Furthermore, the prevalence of moderate or severe malnutrition, as well as Child-Pugh classification B or C, was significantly higher in both groups that did not survive the follow-up (Table 1). Noteworthy however, the present study showed that reduced HGS, considering the cutoff value proposed in this work, was a strong predictor of mortality and 12-month survival for a sample population of adult and elderly male patients suffering with ACLD (Figures 1A and 1B). It is suggested that HGS can be used to predict mortality, similarly to indicators of severity and prognosis already validated and used in clinical practice, such as the Child-Pugh classification and the MELD-Na score.

Based on the outcomes of the Youden (J) index, we have observed that the HGS value that predicted mortality in adults was more sensitive than specific, while the value established for the elderly was the opposite (Fig. 1). This finding suggests that HGS is a good predictor of mortality, but it would be important to consider the patient's age prior to further inferring about the sensitivity and specificity of the method. In Supplementary Table 1 a comparison of cut-off points, sensitivity, specificity, and positive and negative predictive values obtained between the Youden (J) index and the Index of Union (IU) outcomes for the adult and elderly sample population investigated is presented. [(22)]

Our results corroborate published evidence that revealed an association between muscle weakness identified by dynamometry with higher mortality rate and reduced survival in ACLD [(8, 6, 21, 23, 24)]. Daphnee and colleagues [(21)] showed that a HGS of 19.5 kg or lower was associated with 7.8 times more chances of death in a sample population of patients awaiting a liver transplant. Hanai and colleagues showed in a sample population of cirrhotic patients that HGS below 30 kg for men and 15 kg for women were cutoff values that predicted mortality and reduced survival for that population (23).

Additionally, a study recruiting patients suffering with end-stage liver disease showed that muscle strength and performance were better biomarkers to predict mortality as compared to muscle mass. [(24)]. This finding is relevant once HGS is not influenced by the presence of oedema and ascites, common characteristics in individuals with decompensated ACLD. In addition, dynamometry can be performed at the bedside, being an excellent parameter for monitoring hospitalised patients. We suggest that HGS, individually or together with the prognostic indices already validated including Child-Pugh and MELD-Na scores, can be used as a reliable biomarker for clinical and nutritional follow-up of ACLD patients.

Reduced muscle strength has been gaining relevance as a diagnostic tool for sarcopenia. The European Working group on Sarcopenia in Older People has recently updated the diagnostic criteria, recommending that reduced muscle strength be an indicator for the identification of pre-sarcopenia [(25)]. This update has been recommended as muscle strength and function shows a stronger association with negative outcomes as compared to the actual amount of muscle mass, which was a priority indicator used in the definition proposed in the previous consensus [(25, 26, 27)].

We have presented in this study a preliminary analysis of identification and evaluation of HGS cutoff values to predict mortality and survival for male patients, adults and elderly, suffering with ACLD. Our presentation of the stratification of HGS reference values according to age group is a relevant finding as the physiological influence of ageing on muscle strength is well known, and so is its influence in patients diagnosed with compensated (Child-Pugh A) and decompensated (Child-Pugh B+C) ACLD.

A limitation of our study refers to the sample size, once the patient allocation within age groups did not allow for an even number in each group (114 adults *versus* 71 elderly). On the other hand, we have excluded women from the present analysis as to ensure specificity for the cutoff points for the male population, specifically.

The present study examined a convenience sample; however, the participants were recruited from a tertiary referral hospital in the Brazilian northeast. In turn, a generalisation of the HGS reference values identified in the present study may not necessarily be applicable to patients from other countries or regions due to population heterogeneity. A multicentre study which presents HGS cutoff accurate enough to predict mortality in larger populations of ACLD adult and elderly patients of both sexes will bring certainty as to the applicability of our results to larger settings.

In conclusion, the results of the present study show that reduced HGS was associated with increased mortality and reduced survival in ACLD male patients. As dynamometry is a low-cost method and easily reproducible in clinical practice, HGS can be effectively applied for inpatient and outpatient nutritional care. HGS cutoff values may be used to plan a more tailored nutritional therapy and, most importantly, for the early detection of individuals at greater risk of negative outcomes in ACLD. Further validation and consolidation of HGS cutoff values through research in broader settings will confirm their applicability as indicators of nutritional status and mortality predictor in ACLD patients.

Conflict of interest statement

The authors have no conflict of interest to disclose.

Funding

The authors are grateful to the Federal University of Bahia for overall funding for this project. There has not been specific funding for this project.

Author Contributions

Cortes DM was responsible for the conception, design and coordination of the study; acquisition, analysis, and interpretation and discussion of data. Cortes DM performed statistical analyses and drafted the manuscript.

Boulhosa RSSB was responsible for the conception, acquisition, analysis, and interpretation and discussion of data. Boulhosa RSSB performed statistical analyses and drafted the manuscript.

Paz CLSL was responsible for statistical analyses.

Cunha CM was responsible for the analysis, interpretation and discussion of data and drafted the manuscript.

Oliveira LPM was responsible for the analysis, interpretation and discussion of data and drafted the manuscript.

Bueno AA was responsible for the analysis, interpretation and discussion of data and drafted the manuscript.

Lyra AC was responsible for the conception, acquisition, analysis, and interpretation of data.

Jesus RP was responsible for the conception, acquisition, analysis, and interpretation and discussion of data. Jesus RP still performed statistical analyses and drafted the manuscript.

Ethics Committee

This study received full ethical approval by the Research Ethics Committee of university hospital, under registration number 3.380.156

Acknowledgements

The authors wish to express their gratitude to the participants and their families at a difficult and challenging time for them.

Conflict of interest statement:

The authors have no conflic

References

1. Parola M, Pinzani M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. Mol Aspects Med. 2019 Feb;65:37-55. doi: 10.1016/j.mam.2018.09.002. Epub 2018 Sep 13. PMID: 30213667.

2. Maharshi S, Sharma BC, Srivastava S. Malnutrition in cirrhosis increases morbidity and mortality. J Gastroenterol Hepatol. 2015;30(10):1507–13.

3. Khalatbari-Soltani S, Marques-Vidal P. Impact of nutritional risk screening in hospitalized patients on management, outcome and costs: A retrospective study. Clin Nutr [Internet]. 2016;35(6):1340–6. Available from: http://dx.doi.org/10.1016/j.clnu.2016.02.012

4. Carvalho L, Parise ER. Evaluation of nutritional status of nonhospitalized patients with liver cirrhosis. Arq Gastroenterol. 2006; 43(4):269–74.

5. Lai JC, Tandon P, Bernal W, et al. Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology [Internet]. 2021;0–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34233031

6. Plauth M, Bernal W, Dasarathy S, et al. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr [Internet]. 2019; 38(2):485–521. Available from: https://doi.org/10.1016/j.clnu.2018.12.022

7. Merli M, Berzigotti A, Zelber-Sagi S, et al. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol [Internet]. 2019;70(1):172–93. Available from: https://doi.org/10.1016/j.jhep.2018.06.024

8. Tandon P, Low G, Mourtzakis M, Zenith L, Myers RP, Abraldes JG, et al. Um modelo para identificar sarcopenia em pacientes com cirrose. Gastroenterologia Clínica e Hepatologia. 2016;14(10):1473-1480.e3.

9. Nishikawa H, Shiraki M, Hiramatsu A, et al. Reduced Handgrip Strength Predicts Poorer Survival in Chronic Liver Diseases: A Large Multi-Center Study in Japan. Hepatol Res. 2021;(April):1–11.

10. Schlüssel MM, dos Anjos LA, de Vasconcellos MTL, et al. Reference values of handgrip dynamometry of healthy adults: A population-based study. Clin Nutr. 2008;27(4):601–7.

11. Lee YL, Jin H, Lim JY, et al. Relationship Between Low Handgrip Strength and Chronic Kidney Disease: KNHANES 2014-2017. J Ren Nutr [Internet]. 2021;31(1):57–63. Available from: https://doi.org/10.1053/j.jrn.2020.03.002

12. da Silva TK, Perry IDS, Brauner JS, et al. Performance evaluation of phase angle and handgrip strength in patients undergoing cardiac surgery: Prospective cohort study. Aust Crit Care [Internet]. 2018;31(5):284–90. Available from: http://dx.doi.org/10.1016/j.aucc.2017.09.002

13. Ministério da Saúde. Doença Hepática. Man Perícia Médica. 2004;5.

14. Yamashiki N, Sugawara Y, Tamura S, et al. Model for end-stage liver disease and model for end-stage liver disease-na scores predict both before-listing and wait-list mortality. Transplant Proc [Internet]. 2012;44(2):389–92. Available from: http://dx.doi.org/10.1016/j.transproceed.2012.01.037

15. de FREITAS ACT, Rampim AT, Nunes CP, et al. Impact of meld sodium on liver transplantation waiting list. Arq Bras Cir Dig. 2019;32(3):3–7.

16. Hurria A, Cohen HJ, Extermann M. WHO_TRS_854.pdf [Internet]. Vol. 1, Journal of Geriatric Oncology. 2010. p. 40–4. Available from: https://www.analesdepediatria.org/en-tuberculosis-in-paediatric-age-group-articulo-S2341287920302544.

17. Detsky AS, McLaughlin Jr, Baker JP, et al. Qual a avaliação subjetiva global de estado nutricional?. Revista de nutrição parenteral e enteral, v. 11, n. 1, pág. 8-13, 1987.

18. Hillman TE, Nunes QM, Hornby ST, et al. A practical posture for hand grip dynamometry in the clinical setting. Clin Nutr. 2005;24(2):224–8.

19. Sopelete MC, Pesquisa MI. Parte III - Métodos de análise em diferentes tipos de estudos 8. Métodos de análise em estudos sobre diagnóstico. 2005;

20. Glas AS, Lijmer JG, Prins MH, et al. The diagnostic odds ratio: a single indicator of test performance. J Clin Epidemiol. 2003 Nov;56(11):1129-35. doi: 10.1016/s0895-4356(03)00177-x. PMID: 14615004.

21. McDaniel J, Davuluri G, Hill EA, et al. Hyperammonemia results in reduced muscle function independent of muscle mass. Vol. 310, American Journal of Physiology - Gastrointestinal and Liver Physiology. 2016. p. G163–70.

22.Unal I. Defining an Optimal Cut-Point Value in ROC Analysis: An Alternative Approach. Comput Math Methods Med. 2017;2017:3762651. doi: 10.1155/2017/3762651. Epub 2017 May 31. PMID: 28642804; PMCID: PMC5470053.

23. Daphnee DK, John S, Vaidya A, et al. Hand grip strength: A reliable, reproducible, cost-effective tool to assess the nutritional status and outcomes of cirrhotics awaiting liver

transplant. Clin Nutr ESPEN [Internet]. 2017;19:49–53. Available from: http://dx.doi.org/10.1016/j.clnesp.2017.01.011

24. Hanai T, Shiraki M, Imai K, et al. Reduced handgrip strength is predictive of poor survival among patients with liver cirrhosis: A sex-stratified analysis. Hepatol Res. 2019;49(12):1414–26.

25. Sidhu SS, Saggar K, Goyal O, et al. Muscle strength and physical performance, rather than muscle mass, correlate with mortality in end-stage liver disease. Eur J Gastroenterol Hepatol. 2021;555–64.

26. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis. Age Ageing. 2010;39(4):412–23.

27. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31.

Table 1: ACLD patient data at first observation, in retrospect to the 12 months follow-up period.

	Adults (<60 age)			Elderly (≥ 60 age)		
	Survivor (n = 89)	Non-survivor (n = 25)	*P value*	Survivor (n = 58)	Non-survivor (n = 13)	*P value*
Age						
median [IQI]	52 [46 - 57]	54 [50 - 57]	p = 0.387	64 [62 - 70.25]	67 [64 - 72]	p = 0.157
Body Mass Index						
Mean ± SDM	25.13 ± 1.17	26.16 ± 1.23	p = 0.374	26.16 ± 4.32	25.83 ± 5.05	p = 0.812
Handgrip strength						
Mean ± SDM	28.55 ± 9.34	24.45 ± 7.95	**p = 0.048**	24.19 ± 8.73	18.68 ± 7.51	**p = 0.031**
MELD-Na						
median [IQI]	10 [8 - 12]	10.5 [9 - 16.25]	p = 0.256	9 [7 - 11]	11 [10 - 15]	**p = 0.024**
MELD						
median [IQI]	10 [8 - 12.7]	13.5 [10 - 20]	**p = 0.000**	9 [7 - 11]	10 [8 - 16]	**p = 0.041**
Subjective Global						

Assessment						
Well-nourished	54 (47,8%)	6 (5,3%)	**p = 0.001**	40 (57,1%)	3 (4,3%)	**p = 0.003**
Moderately / severely malnourished	34 (30,1%)	19 (16,8%)		17 (24,3%)	10 (14,3%)	
Child-Pugh classification						
Child-Pugh A	41 (37,6%)	1 (0,9%)	**p <0.001**	36 (51,4%)	4 (5,7%)	**p = 0.002**
Child-Pugh B + C	44 (40,4%)	23 (21,1%)		21 (30,0%)	9 (12,9%)	
Aetiology*						
Alcoholic	54 (47,4%)	11 (9,6%)		30 (42,2%)	7 (9,9%)	
Viral	22 (19,3%)	4 (3,5%)	**p =0.020**	19 (26,8%)	3 (4,2%)	**p = 0.702**
*Other***	13 (11,4%)	10 (8,8%)		9 (12,7%)	3 (4,2%)	

Legend: SDM: standard deviation of the mean; IQI: interquartile interval; MELD-Na: Model for End-Stage Liver Disease–Sodium. Data were expressed in number of patients (%). * Analysis corrected by bootstrapping implementation. **breakdown of aetiologies presented in supplementary table 2.

Table 2. Predictive variables of survival according to the COX regression model – Univariate and Multivariate

Univariate analysis				
	HR	95.0% CI to HR		p value
		Inferior	Superior	
Reduced HGS	3.515	1.663	7.432	0.001
Child-Pugh B+C	6.325	2.462	16.244	0.000
Child-Pugh A	0.158	0.062	0.406	.000
MELD-Na	1.158	1.066	1.259	0.001
Multivariate analysis				
	HR	95.0% CI to HR		p value
		Inferior	Superior	
Reduced HGS	2.755	1.294	5.866	0.009
Child-Pugh B+C	5.488	2.127	14.162	0.000
Reduced HGS	2.755	1.294	5.866	0.009
Child-Pugh A	0.182	0.071	0.470	.000
Reduced HGS	3.385	1.442	7.945	0.005
MELD-Na	1.148	1.055	1.250	0.001

Legend: HGS: handgrip strength; HR: Hazard Ratio; CI: confidence interval;

MELD-NA: Model for End-Stage Liver Disease-Sodium.

Figure 1. Handgrip Strength (HGS) reference values to predict mortality in ACLD male patients, based on age group. Figure 1A: Adults. Figure 1B: Elderly. Receiver Operating Characteristic Curve (ROC): HGS vs. mortality. Area under the curve (AUC)

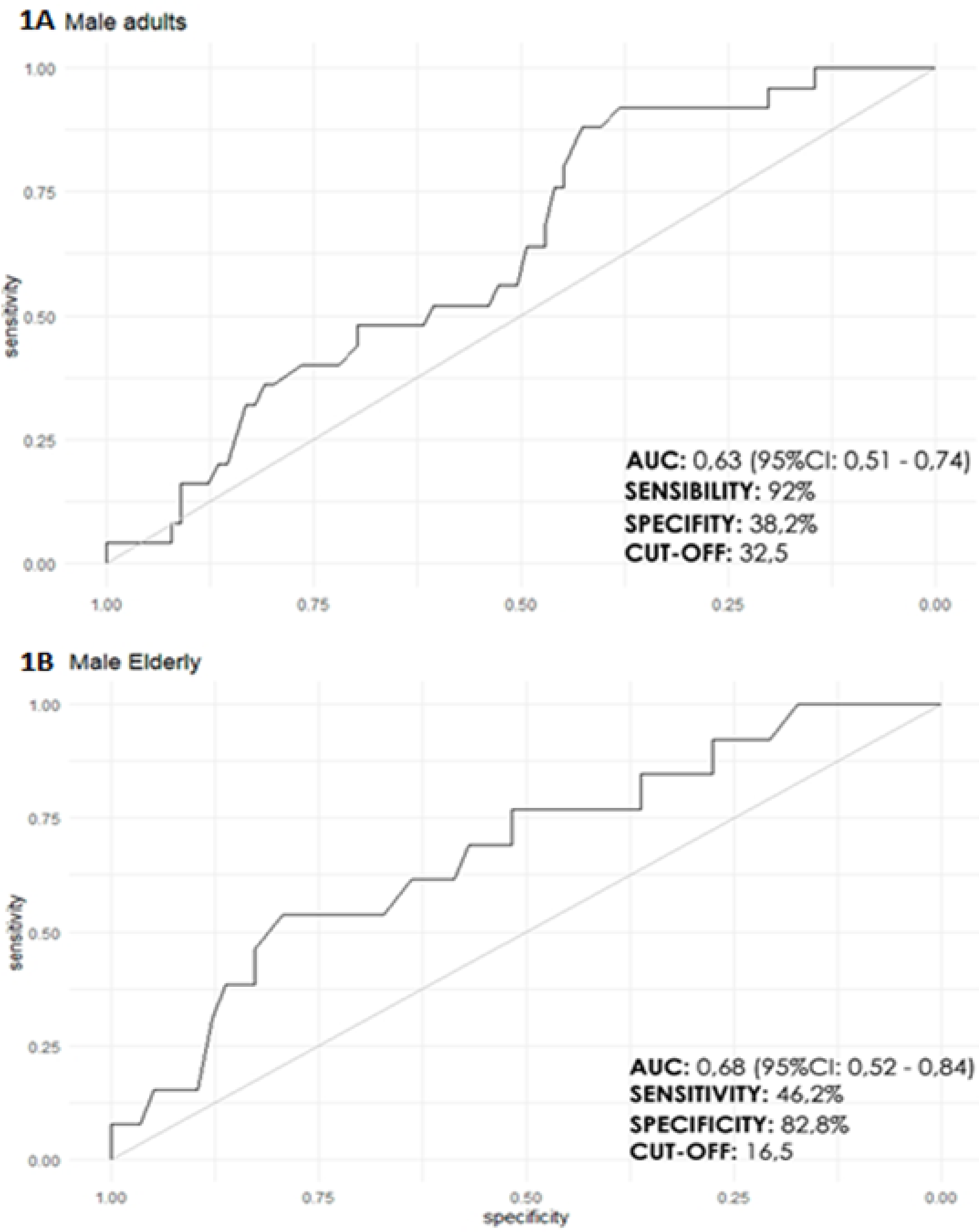
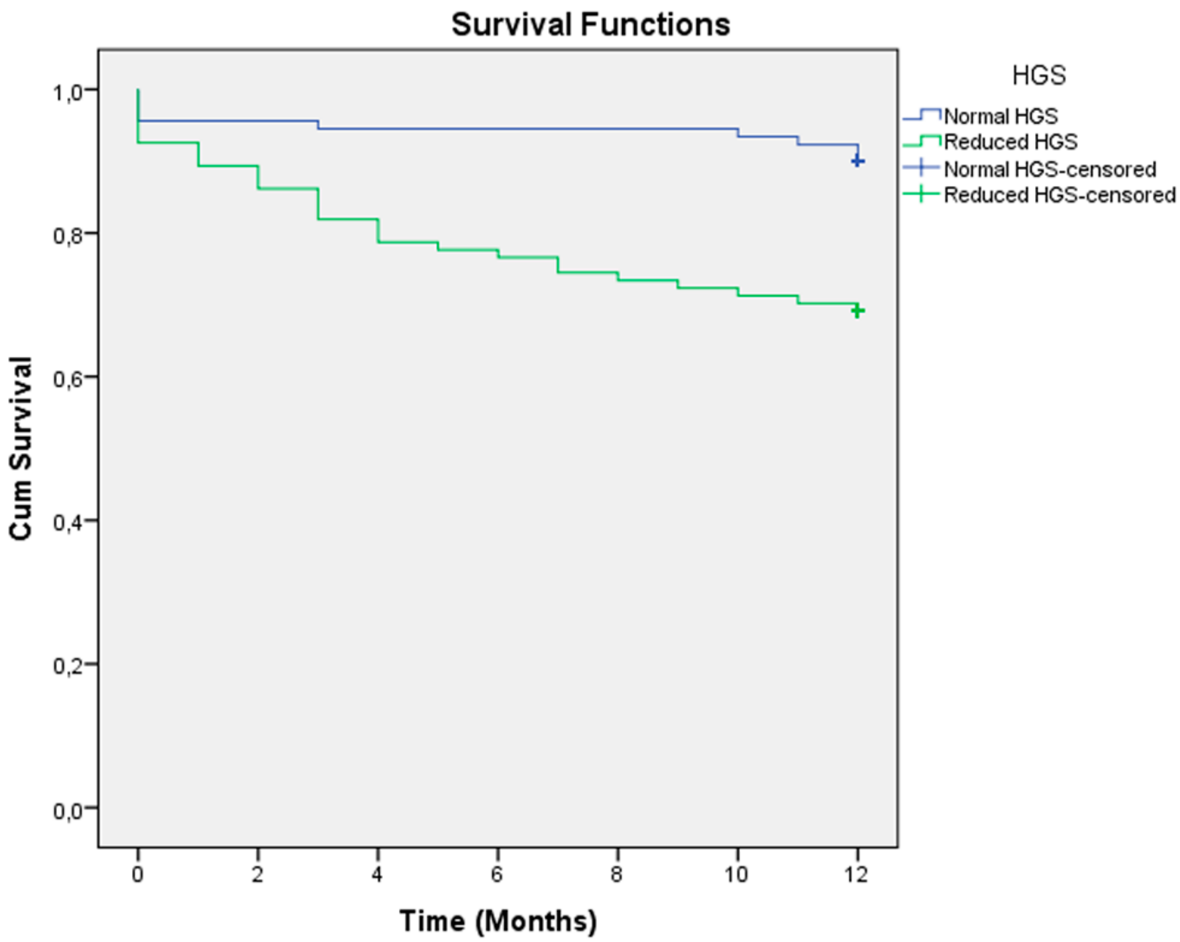


Figure 2. Kaplan-Meier curve of the entire sample population. Curves with description of "adequate censored" and "inadequate censored" refer to individuals who remained alive in both groups.


Survival Functions
HGS
Normal HGS
Reduced HGS
Normal HGS-censored
Reduced HGS-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
2
4
6
8
10
12
Time (Months)