

Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>
doi: 10.17554/j.issn.2224-3992.2022.11.1037

Journal of GHR 2022 February 21; **11**(1): 3652-3657
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

REVIEW

Hepatic Cirrhosis and Physical Activity: A Guide for the Clinical Practice

Diane Michela Nery Henrique¹, Carla Malaguti², Carlos Alberto Mourao-Junior³, Daniel Godoy Martinez⁴, Fabio Heleno de Lima Pace³, Giovanna Pereira Neiva Boechat da Rocha³, Mateus Camaroti Laterza⁴, Tarsila Campanha da Rocha Ribeiro³, Tuany Mageste Limongi⁴, Cristiane de Souza Bechara³, Julio Maria Fonseca Chebli³

1 Department of Medicine, University Hospital, Federal University of Juiz de Fora, University of Juiz de Fora School of Medicine, Minas Gerais, Brazil;

2 Physiotherapy Department, Federal University of Juiz de Fora, University of Juiz de Fora School of Physiotherapy, Minas Gerais, Brazil;

3 Division of Gastroenterology, Department of Medicine, University Hospital, Federal University of Juiz de Fora, University of Juiz de Fora School of Medicine, Minas Gerais, Brazil;

4 Cardiovascular Research Unit and Exercise Physiology, University Hospital and Faculty of Physical Education and Sports, Federal University of Juiz de Fora, Juiz de Fora, MG.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (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: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Julio Maria Fonseca Chebli, Division of Gastroenterology, Department of Medicine, University Hospital, Federal University of Juiz de Fora, University of Juiz de Fora School of Medicine, Minas Gerais, Brazil.

Telephone: +55 (32) 2102-3841

Email: chebli@globo.com

Received: December 2, 2021

Revised: December 28, 2021

Accepted: January 1, 2022

Published online: February 21, 2022

ABSTRACT

Patients with liver cirrhosis have impaired physical fitness involving several multifactorial mechanisms, such as sarcopenia, hyperdynamic

circulatory status, and hepatopulmonary syndrome, in addition to sedentary behavior. The reduction in exercise tolerance is related to the degree of impairment of liver function in these patients. Therefore, the assessment of exercise capacity has been shown to be valid as a measure of prognostic value and to predict the clinical risk of decompensation. This review briefly shows the importance of evaluating exercise functional capacity in cirrhotic patients, as well as highlights how exercise and physical activity programs are safe and effective in improving muscle mass, increasing exercise capacity, and reducing the pressure gradient hepatic venous. It is expected that the assessment of the functional physical status of cirrhotic patients and their encouragement to engage in exercise programs and increased physical activity will be encouraged in clinical practice.

Key words: Hepatic cirrhosis; Physical activity; Clinical practice

© 2022 The Authors. Published by ACT Publishing Group Ltd. All rights reserved.

Henrique DMN, Malaguti C, Mourao-Junior CA, Martinez DG, de Lima Pace FH, da Rocha GPNB, Laterza MC, da Rocha Ribeiro TC, Limongi TM, de Souza Bechara C, Chebli JMF. Hepatic Cirrhosis and Physical Activity: A Guide for the Clinical Practice. *Journal of Gastroenterology and Hepatology Research* 2022; **11**(1): 3652-3657 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/3261>

INTRODUCTION

Liver cirrhosis is a prevalent disease that currently ranks among the leading causes of global mortality, and 2.4 % of all deaths in the world occurred due to its complications in 2017^[1]. Chronic hepatitis B and C, alcoholic liver disease, and fatty liver disease associated with metabolic dysfunction (MAFLD) are the most common etiologies^[1], the latter of increasing incidence.

Different agents and mechanisms can cause chronic and insidious aggression by inflammation, cell necrosis, and activation of hepatic fibrogenesis responsible for the synthesis of extracellular matrix, being hepatic stellate cells a key element in this process. Furthermore, with the progressive deposition of collagen matrix in the liver parenchyma, there is the formation of fibrotic nodules and distortion

of the vascular architecture that results in the loss of the organ's functional capacity and the development of portal hypertension, ultimately responsible for the morbidity and mortality observed in this group of patients^[2,3].

Currently, among the complications of chronic liver disease, such as ascites, hepatic encephalopathy, and variceal bleeding, sarcopenia and frailty have been highlighted. These are interrelated conditions, with sarcopenia being defined as a reduction in muscle volume and strength and frailty as a condition in which there is a low physiological reserve and high vulnerability to health stressors^[4]. Sarcopenia is a common finding among the elderly and is present in several chronic diseases, but individuals with chronic liver disease are especially predisposed^[5]. In patients with liver cirrhosis, sarcopenia contributes to both the reduction in physical performance and exercise capacity, which are related to adverse outcomes^[4].

Common conditions within the spectrum of chronic diseases, and present in liver fibrosis, such as malnutrition, persistent chronic inflammatory state, changes in metabolism, and sedentary lifestyle are added to cause a reduction in the ability to carry out physical activities and exercises per contributing to the impairment of peripheral muscles^[6]. Furthermore, systemic disturbances can affect the heart, lungs, kidneys, and other organ systems in chronic liver disease^[7]. Therefore, the impairment of physical fitness is multifactorial in these patients involving several mechanisms as sarcopenia^[6], the hyperdynamic circulatory state^[8], and hepatopulmonary syndrome^[9].

ASSESSMENT OF FUNCTIONAL CAPACITY IN CIRRHOTIC PATIENTS

Since physical fitness is a broad and complex concept, the ability of the heart and lungs to meet the metabolic demand of skeletal muscles is used to assess an individual's exercise capacity and functionality. The capacity for aerobic exercise, that is, the use of oxygen during the physical effort and the functional capacity to perform activities of daily living, are aspects of physical condition that can be evaluated through specific and validated tests^[10]. The most common tests used in the cirrhotic population are the cardiopulmonary exercise test (CPET) and the six-minute walk test (6MWT)^[6].

CPET is considered the gold standard for addressing exercise capacity by measuring a series of variables related to the body's ability to capture, transport, and use oxygen^[11,12]. In the CPET, an exercise is performed on a treadmill or cycle ergometer, gradually increasing intensity until exhaustion or the appearance of limiting signs and symptoms. During exercise, clinical signs and symptoms, heart rate (HR), electrocardiogram, and blood pressure (BP) are monitored. In addition, respiration is evaluated through a gas analyzer, allowing the measurement of ventilation, oxygen consumption, and carbon dioxide production^[13]. Usually, in this approach, the measurement of the peak of oxygen uptake (Peak VO₂) and the first ventilatory threshold, also known as the anaerobic threshold (AT), stand out. The Peak VO₂ value corresponds to the maximum load of effort tolerated by the individual. Thus, it is, at least partially, influenced by the effort of the tested patient to perform this effort. Conversely, the AT corresponds to the graphic manifestation of the beginning of the change from aerobic to anaerobic metabolism and is a submaximal measure that does not depend on the individual's effort to perform a maximum test^[11].

The 6MWT is a technically less complex assessment, performed in a flat 30-meter stretch of an unimpeded walkway. Monitoring of clinical signs and symptoms, BP, HR, and oxygen saturation is

effectuated through a pulse oximeter during the six minutes that the patient walks at the fastest possible pace, but without running, according to his physical condition. Standardized instructions are given before starting the test, and verbal feedback is given every minute, as recommended by the American Thoracic Society guidelines. At the end of six minutes, the total distance walked is calculated due to the test^[14]. The 6MWT is a submaximal exercise test that has been shown to have good reliability when used to assess the functional capacity of cirrhotic patients^[15], in addition to correlating with the functional capacity assessed by CPET^[16,17]. In addition, the 6MWT has the advantages of being easy to be operated by the examiner, has low cost, and presents minimal risk to the patient. Therefore, it is a valid alternative for the evaluation of cirrhotic patients in any scenario.

Previous studies have shown that patients with cirrhosis have a 40% to 50% reduction in oxygen consumption than their healthy sedentary peers^[16,18]. In addition, these patients showed a reduction in exercise tolerance, which is associated with the degree of liver function impairment^[15,18,19].

CLINICAL IMPLICATIONS OF REDUCED FUNCTIONAL CAPACITY IN CIRRHOSIS

Several studies with cirrhotic patients point toward a direct relationship between physical fitness and prognosis^[17,20], following the line of studies that demonstrated that low physical fitness is associated with more significant morbidity and mortality from all causes in the presence of various chronic diseases. Furthermore, over the past few years, studies have shown that the assessment of functional capacity in cirrhotic patients presents itself as a valuable tool to assess survival^[15,17], the prognosis before and after liver transplantation^[11-12,21-21], and, more recently, the risk of clinical decompensation^[20].

Alameri and colleagues^[15] showed that the distance covered in the 6MWT by patients with chronic liver disease was shorter than that covered by healthy individuals. Furthermore, this distance was even shorter when patients were already in the stage of established cirrhosis. The 98 cirrhotic patients in this study were followed up on an average follow-up of 42 weeks (SD \pm 13 weeks), and 15% of them died from complications of liver disease during this follow-up period. The Kaplan-Meier survival curve was used to evaluate these patients in terms of distance walked on the 6MWT, and the log-rank test demonstrated that cirrhotic patients who walked less than 250 m had a lower survival (P : 0.021). Thus, the authors identified this tool as capable of producing an additional prognostic marker in patients with liver cirrhosis, as it was an independent predictor of survival in this group of patients.

Carey et al. linked the distance walked on the 6MWT with survival in liver transplant candidates with MELD score above 15, at a mean follow-up time of 148 days^[21]. This study showed that 6MWT distance was significantly associated with mortality. A distance below 250 m was a predictor of increased risk of death for those cirrhotic patients on the waiting list for the procedure. In particular, a 52% reduction in mortality was noted for every 100 m increase in baseline 6MWT [HR 0.48, 95% CI: 0.33-0.67, p < 0.0001 for every 100 m increase in distance walked]. Distance on the 6MWT was an independent predictor of mortality in transplant candidates, even after adjustments for age and MELD score, and could identify candidates at higher risk of death on the waiting list.

A study published by Bernal et al. evaluated the relationship between aerobic fitness parameters, determined by CPET

performed by elective indication in the preoperative period of liver transplantation, and 1-year mortality after CPET for patients not undergoing transplantation during this period and also the 1-year mortality after transplant in those submitted to the procedure^[11]. This study included 399 cirrhotic patients referred for transplantation, although some of them were declined from the procedure according to the assessment of the clinical staff of the referral hospital. The CPET parameters considered were Peak VO₂ and AT. The authors demonstrated a clear relationship between aerobic fitness and survival in patients who underwent and those who did not undergo liver transplantation within a one-year follow-up. Additionally, the AT's superiority was found compared to the Peak VO₂ to predict mortality, although without establishing an exact value of the AT to discriminate survivors from non-survivors.

Ow *et al.* examined the association between maximal exercise capacity and survival in transplant waiting list patients also found the potential of CPET in predicting 90-day free-transplant mortality^[22]. The Peak VO₂ was significantly lower among non-survivors (15.2 versus 21.2 mL/min.min-1; $p < 0.001$). Peak VO₂ had a good performance for this sample with an area under the curve of 0.84 (95% CI, 0.76-0.92, sensitivity: 90%, specificity: 74%; $p < 0.001$). The cutoff value established to predict mortality was < 17.6 mL/minute.kg-1. The authors concluded that patients evaluated for liver transplantation with greater impairment of functional capacity have a lower short-term survival rate; this is particularly true for individuals with more severe liver disease.

In the same line of investigation, patients with chronic liver disease who were potential candidates for liver transplantation underwent CPET and 6MWT^[9]. An evaluation of the three-year survival curve showed that patients with values below 17 mL/kg/min had a survival rate of 55% compared with 94% survival for those who reached values > 17 mL/kg/min on the CPET. In addition, individuals who walked less than 410 m on the 6MWT had a lower survival rate (55%) compared to the 97% survival rate of those who walked more than that. Thus, in this study, the distance walked on the 6MWT and the Peak VO₂ were independent predictors of mortality.

In a systematic review on the subject^[12], researchers collected data to better establish the predictive value of CPET as a tool to assess maximal exercise capacity in cirrhotic patients before and after liver transplantation. Five studies focused on the Peak VO₂

and TA, two studies only on Peak VO₂, and a single study evaluated the oscillation curve of ventilation during exercise. The researchers found that the studies support CPET as an objective and independent predictor of pre-and post-transplant mortality. However, some drawbacks of this review need to be pointed out as the heterogeneity of included studies, different CPET parameters, CPET cutoff values, and follow-up time, not making it possible to satisfactorily identify specific cutoff values related to pre-and post-transplant mortality based on the analyzed data.

More recently, our research group dedicated itself to investigating the relationship between functional capacity and clinical decompensation in cirrhotic patients^[20] (19). Since the primary determinant of survival in patients with cirrhosis is the development of decompensation^[23], we decided to investigate the ability of the 6MWT as a predictor of the risk of clinical decompensation (i.e., jaundice, ascites, bleeding from esophageal varices, spontaneous bacterial peritonitis or hepatic encephalopathy) in clinically compensated cirrhotic patients. Therefore, a cohort of 55 cirrhotic patients was followed up for 12 months (mean age 56.3 years, 65% male, 65% Child-Pugh class A and 35% Child-Pugh class B) after the 6MWT. In the studied sample, the 6MWT predicted the highest risk of developing clinical decompensation of cirrhosis in the one-year follow-up for those patients who walked less than 401.8 meters (sensitivity of 64% and specificity of 82%). In addition, we also found data indicating that, at one-year follow-up, worse performance on the 6MWT was able to predict a greater need for hospitalization due to clinical decompensation of the disease.

Finally, the currently published literature supports the importance of assessing functional capacity in the clinical follow-up of cirrhotic patients and raises the question of the value of recommending regular physical activity for these individuals to improve patients' physical fitness and, consequently, the prognosis.

PHYSICAL ACTIVITY AND LIVER CIRRHOSIS

Several health associations have indicated the regular practice of physical exercise as a non-pharmacological strategy for preventing and treating chronic diseases. This clinical approach even has a positive impact on reducing the probability of death. In a study carried out in the United States of America, with almost 480 thousand

Table 1 Pre-exercise safety evaluation and exercise schedule suggested for cirrhotic patients Pre-exercise safety assessment.

Cirrhosis related safety screening	High-risk varices: prophylaxis needs
	Hepatic encephalopathy, ascites: optimize supervision by caregivers
Assess physiological competence	Assess for fall risk, musculoskeletal limitations
Cardiopulmonary safety screening	
Exercise Prescription – FITT* Recommendations	
Frequency	Aerobic: 4-7 d/week;
	Resistance: 2-3 d/week;
	Flexibility and balance: 2-3 d/week
Intensity	Borg scale: moderate intensity 3-5/10
	Talk test: able to speak in full sentences but still notices laboured breath
Type	Aerobic: build to 150 minutes per week. The very deconditioned may need to start with 1-min of walking followed by 1-min of rest.
	Resistance: 3 sets of 10-15 repetitions.
	Flexibility and balance: 1 set of 3 repetitions
Time	Aerobic: walking is the most universal aerobic intervention
	Resistance: functional (e.g. stairs) or progressive weight/band training
	Flexibility and balance: stretching and balance exercises

* FITT (Frequency, Intensity, Type, Time); Adapted from Tandon P *et al.* J Hepatol. 2021; 75 Suppl 1:S147-S162. [25]

North Americans followed for nine years, the practice of aerobic, resistance, or both physical exercises reduce, on average, up to 0.60 the risk relative of all-cause mortality^[24].

Exercise programs ranging from 8-14 weeks in duration have showed improvements in peak exercise capacity, muscle mass, muscle strength, quality of life and fatigue^[25]. Ideally, all patients with decompensated cirrhosis should receive pre-exercise safety evaluation and an exercise instruction as suggested in Table 1. Usually, resistance training is the target of many exercise programs in patients with decompensated cirrhosis, with aerobic training introduced subsequent. If falls are a concern issue, initial priority is often placed on lower extremity strength and balance training^[25].

In a study developed by Bacchi E., patients with nonalcoholic fatty liver disease and type 2 diabetes were randomized for moderate-intensity aerobic exercise training or resistance exercise training. After a 4-month period, the groups similarly decreased body mass index, glycated hemoglobin levels, and liver fat content. Additionally, it was possible to note that hepatic steatosis, defined as hepatic fat content greater than 5.56%, disappeared in approximately 25% of people^[26]. Likewise, in a cross-sectional analysis of a representative sample of the North American population, it was shown that people who followed the national recommendations for the practice of physical activities had a lower chance of developing nonalcoholic fatty liver disease. Indeed, people who performed more than 300 minutes of weekly physical activity had a 63% reduced risk of developing liver cirrhosis^[27]. These findings allow us to infer that a physically active lifestyle can prevent or at least attenuate risk factors for the development of liver cirrhosis.

Regarding the management of people with liver cirrhosis, physical training has been receiving critical attention. After only eight weeks of supervised aerobic physical training of moderate-intensity, cirrhotic patients, classified as Child-Pugh A and B, increased the VO₂ peak, the distance covered in the 6MWT, the thigh circumference, and decreased the fatigue index. Even without modifying the biochemical parameters, no adverse effects were reported throughout the physical training protocol^[28]. However, it is noteworthy that in this study, the patients were stable, underwent cardiopulmonary testing, and, when necessary, underwent primary prophylaxis to prevent bleeding from esophageal varices. Moreover, Román *et al.* demonstrated that 12 weeks of aerobic exercise training associated with resistance was effective in increasing lean mass and decreasing fat mass of patients with liver cirrhosis evaluated by body composition through dual-energy X-ray absorptiometry, contributing to justify, at least in part, the observed decrease in the risk of falling in these patients^[29].

In association with improved functional capacity and body composition, physical training can also change hepatic hemodynamics. After 14 weeks of supervised aerobic physical training of moderate-intensity, associated with muscle strengthening, coordination, and balance exercises, stable patients with liver cirrhosis had an average decrease in the hepatic venous pressure gradient by 2.5 mmHg, a fact that was not observed in the control group. In this study, all patients were evaluated and monitored from a cardiological and hepatic point of view. No episode of variceal bleeding or hepatic encephalopathy was recorded during this follow-up^[30]. Also, regarding portal pressure, a 16-week intervention for lifestyle modification, consisting of a low-calorie diet associated with moderate-intensity aerobic exercise training, was effective in decreasing at least 10% of the hepatic venous pressure gradient in 42% of patients. A decrease of at least 20% in this gradient was observed in 24% of patients with liver cirrhosis and portal hypertension^[31].

As the functional capacity is directly associated with the severity of the liver disease, patients with liver cirrhosis with an indication for liver transplantation have a significant deficit in the functional capacity. And, as in other chronic conditions, the prescription of physical exercise seems to be an exciting approach for people on the waiting list for a liver transplant. A study developed by Morkane *et al.* demonstrated the excellent feasibility of a physical exercise program for patients with liver cirrhosis on the transplant waiting list. In this prospective cohort, patients significantly improved their functional capacity, expressed as an increase in peak VO₂, after six weeks of the proposed aerobic exercise training program. However, 44% of patients could not complete the intervention period, none of the cases linked to exercise. In addition, no adverse events related to physical training were reported^[32].

Through these findings, it is possible to suggest that physical exercise should be the approach adopted in the prevention and treatment of chronic liver diseases. For safety, we suggest a careful and multidisciplinary evaluation to include patients in supervised physical training programs.

CONCLUSIONS

Patients with liver cirrhosis have a multifactorial reduction in exercise tolerance, and this impairment is related to the prognosis of the disease. According to this, it seems reasonable to seek access to the functional capacity of these patients as a complementary method of the clinical assessment in liver cirrhosis. For this evaluation, the CPET and the 6MWT are two already validated tools in this population. Furthermore, to offer a safe, tolerable and effective rehabilitation program to this population, it is crucial to understand several points as the clinical pathophysiology of exercise in this health condition, systemic repercussions of exertion, and potential risks and benefits of physical activity exercise. Finally, although there are barriers to the practice of physical exercise in patients with liver cirrhosis, there is the current knowledge of its effectiveness and safeness. Likewise, it is up to the practicing clinician to encourage and direct their patients to exercise under the supervision of a multidisciplinary team.

REFERENCES

1. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, Poustchi H, Tsoi D, Colombara DV, Abdoli A, Adedoyin RA, Afarideh M, Agrawal S, Ahmad S, Ahmadian E, Ahmadvipour E, Akinyemiju T, Akunna CJ, Alipour V, Almasi-Hashiani A, Almulhim AM, Al-Raddadi RM, Alvis-Guzman N, Anber NH, Angus C, Anoushiravani A, Arabloo J, Araya EM, Asmelash D, Ataeinia B, Ataro Z, Atout MMW, Ausloos F, Awasthi A, Badawi A, Banach M, Ramirez DFB, Bhagavathula AS, Bhala N, Bhattacharyya K, Biondi A, Bolla SR, Boloor A, Borzi AM, Butt ZA, Cámara LLAA, Campos-Nonato IR, Carvalho F, Chu DT, Chung SC, Cortesi PA, Costa VC, Cowie BC, Daryani A, Courten B, Demoz GT, Desai R, Dharmaratne SD, Djalalinia S, Do HT, Dorostkar F, Drake TM, Dubey M, Duncan BB, Effiong A, Eftekhari A, Elsharkawy A, Etemadi A, Farahmand M, Farzadfar F, Fernandes E, Filip I, Fischer F, Gebremedhin KBB, Geta B, Gilani SA, Gill PS, Gutierrez RA, Haile MT, Haj-Mirzaian A, Hamid SS, Hasankhani M, Hasanzadeh A, Hashemian M, Hassen HY, Hay SI, Hayat K, Heidari B, Henok A, Hoang CH, Hostiuc M, Hostiuc S, Hsieh VCR, Igumbor EU, Ilesanmi OS, Irvani SSN, Balalami NJ, James SL, Jeemon P, Jha RP, Jonas JB, Jozwiak JJ, Kabir A, Kasaeian A, Kassaye HG, Kefale AT, Khalilov R, Khan MA, Khan EA, Khater A, Kim YJ, Koyanagi A, Vecchia CL, Lim LL,

- Lopez AD, Lorkowski S, Lotufo PA, Lozano R, Razek MMAE, Mai HT, Manafi N, Manafi A, Mansournia MA, Mantovani LG, Mazzaglia G, Mehta D, Mendoza W, Menezes RG, Mengesha MM, Meretoja TJ, Mestrovic T, Miazgowski B, Miller TR, Mirrahimov EM, Mithra P, Moazen B, Moghadaszadeh M, Mohammadian-Hafshejani A, Mohammed S, Mokdad AH, Montero-Zamora PA, Moradi G, Naimzada MD, Nayak V, Negoi I, Nguyen TH, Ofori-Asenso R, Oh IH, Olagunju, Padubidri JR, Pakshir K, Pana A, Pathak M, Pourshams A, Rabiee N, Radfar A, Rafiei A, Ramezanzadeh K, Rana SMM, Rawaf S, Rawaf DL, Reiner Jr RC, Roeveer L, Room R, Roshandel G, Safari S, Samy AM, Sanabria J, Sartorius B, Schmidt MI, Senthilkumaran S, Shaikh MA, Sharif M, Sharifi A, Shigematsu M, Singh JA, Soheili A, Suleria HAR, Teklehaimanot BF, Tesfay BE, Vacante M, Vahedian-Azimi A, Valdez PR, Vasankari TJ, Vu GT, Waheed Y, Weldegewergs KG, Werdecker A, Westerman R, Wondafrahs DZ, Wondmieneh AB, Yeshitila YG, Yonemoto N, Yu C, Zaidi A, Zarghi A, Zelber-Sagi S, Zewdie KA, Zhang ZJ, Zhao XJ, Naghavi M, Malekzadeh R. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020; **5**: 245-266. [PMID: 31981519]; [PMCID: PMC7026710]; [DOI: 10.1016/S2468-1253(19)30349-8]
2. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014; **383**: 1749-61. [PMID: 24480518]; [DOI: 10.1016/S0140-6736(14)60121-5]
3. Bernardi M, Caraceni P. Novel perspectives in the management of decompensated cirrhosis. *Nat Rev Gastroenterol Hepatol* 2018; **15**(12): 753-764. [PMID: 30026556]; [DOI: 10.1038/s41575-018-0045-2]
4. Tandon P, Montano-Loza AJ, Lai JC, Dasarathy S, Merli M. Sarcopenia and frailty in decompensated cirrhosis. *J Hepatol* [Internet]. 2021; **75**: S147-62. [PMID: 34039486]; [DOI: 10.1016/j.jhep.2021.01.025]
5. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cyrus Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing*. 2019; **48**(1): 16-31. [PMID: 30312372]; [PMCID: PMC6322506]; [DOI: 10.1093/ageing/afy169]
6. Duarte-Rojo A, Ruiz-Margáin A, Montañó-Loza AJ, Mancías-Rodríguez RU, Ferrando A, Kim WR. Exercise and physical activity for patients with end-stage liver disease: Improving functional status and sarcopenia while on the transplant waiting list. *Liver Transplantation* 2018; **24**: 122-139 [PMID: 29024353]; [DOI: 10.1002/lt.24958]
7. Moller S, Kimer N, Barlose M, Bendtsen F. Pathophysiological-based treatments of complications of cirrhosis. *Scand J Gastroenterol* 2020; **55**: 383-94. [PMID: 32233873]; [DOI: 10.1080/00365521.2020.1744709]
8. Moller S, Bendtsen F, Henriksen JH. Splanchnic and systemic hemodynamic derangement in decompensated cirrhosis. *Canadian Journal of Gastroenterology* 2001; **15**: 94-106. [PMID: 11240379]; [DOI: 10.1155/2001/603012]
9. Pereira JLF, Galant LH, Garcia E, Brandão ABM, Marroni CA. Exercise capacity of cirrhotic patients with hepatopulmonary syndrome. *Annals of Hepatology* 2015; **14**: 361-8. [PMID: 25864217]
10. Williams FR, Berzigotti A, Lord JM, Lai JC, Armstrong MJ. Review article: impact of exercise on physical frailty in patients with chronic liver disease. *Alimentary pharmacology & therapeutics* 2019; **50**: 988-1000. [PMID: 31502264]; [DOI: 10.1111/apt.15491]
11. Bernal W, Martín-Mateos R, Lipcsey M, Tallis C, Woodsford K, McPhail MJ, Willars C, Auzinger G, Sizer E, Heneghan M, Cottam S, Heaton N, Wendon J. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. *Liver Transpl* 2014; **20**: 54-62. [PMID: 24136710]; [DOI: 10.1002/lt.23766]
12. Ney M, Haykowsky MJ, Vandermeer B, Shah A, Ow M, Tandon P. Systematic review: pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates. *Aliment Pharmacol Ther*. 2016; **44**: 796-806. [PMID: 27539029]; [DOI: 10.1111/apt.13771]
13. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. *Postgrad Med J*. 2007; **83**: 675-82. [PMID: 17989266]; [PMCID: PMC2734442]; [DOI: 10.1136/hrt.2007.121558]
14. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 111-7. [PMID: 12091180]; [DOI: 10.1164/ajrccm.166.1.at1102]
15. Alameri HF, Sanai FM, Al Dukhayil M, Azzam NA, Al-Swat KA, Hersi AS, Abdo AA. Six Minute Walk Test to assess functional capacity in chronic liver disease patients. *World Journal of Gastroenterology* 2007; **13**: 3996-4001. [PMID: 17663517]; [PMCID: PMC4171175]; [DOI: 10.3748/wjg.v13.i29.3996]
16. Beyer N, Aadahl M, Strange B, Kirkegaard P, Hansen BA, Mohr T, Kjaer M. Improved physical performance after orthotopic liver transplantation. *Liver Transpl Surg* 1999; **5**: 301-9. [PMID: 10388503]; [DOI: 10.1002/lt.500050406]
17. Pereira JLF, Galant LH, Rossi D, Rosa LHT, Garcia E, Brandão ABM, Marroni CA. Functional capacity, respiratory muscle strength, and oxygen consumption predict mortality in patients with cirrhosis. *Canadian Journal of Gastroenterology and Hepatology* 2016; **2016**: 6940374 [PMID: 27559536]; [PMCID: PMC4983318]; [DOI: 10.1155/2016/6940374]
18. Campillo B, Fouet P, Bonnet JC, Atlan G. Submaximal oxygen consumption in liver cirrhosis. Evidence of severe functional aerobic impairment. *J Hepatol* 1990; **10**: 163-7. [PMID: 2332586]; [DOI: 10.1016/0168-8278(90)90046-t]
19. Dharancy S, Lemyze M, Boleslawski E, Neviere R, Declercq N, Canva V, Wallaert B, Mathurin P, Pruvot FR. Impact of impaired aerobic capacity on liver transplant candidates. *Transplantation* 2008; **86**: 1077-83. [PMID: 18946345]; [DOI: 10.1097/TP.0b013e318187758b]
20. Henrique DMN, Malaguti C, Limongi TM, Siqueira MR, Patricie TMF, Mira PAC, Laterza MC, Mourão-Júnior CA, Pace FHL, Chebli JMF. Six-Minute Walking Test as a Predictor of Clinical Decompensation in Patients with Cirrhosis. *J Gastrointest Liver Dis* 2021; **30**: 103-9. [PMID: 33548126]; [DOI: 10.15403/jgld-3122]
21. Carey EJ, Steidley DE, Aqel BA, Byrne TJ, Mekeel KL, Rakela J, Vargas HE, Douglas DD. Six-minute walk distance predicts mortality in liver transplant candidates. *Liver Transpl* 2010; **16**: 1373-8. [PMID: 21117246]; [DOI: 10.1002/lt.22167]
22. Ow MM, Erasmus P, Minto G, Struthers R, Joseph M, Smith A, Warshaw UM, Cramp ME, Cross TJ. Impaired functional capacity in potential liver transplant candidates predicts short-term mortality before transplantation. *Liver Transpl* 2014; **20**: 1081-8. [PMID: 24805969]; [DOI: 10.1002/lt.23907]
23. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017; **65**: 310-335. [PMID: 27786365]; [DOI: 10.1002/hep.28906]
24. Zhao M, Veeranki SP, Magnussen CG, Xi B. Recommended physical activity and all cause and cause specific mortality in US adults: prospective cohort study. *BMJ*. 2020 Jul 1; **370**: m2031. [PMID: 32611588]; [PMCID: PMC7328465]; [DOI: 10.1136/bmj.m2031]

25. Tandon P, Montano-Loza AJ, Lai JC, Dasarathy S, Merli M. Sarcopenia and frailty in decompensated cirrhosis. *J Hepatol.* 2021; **75 Suppl 1**: S147-S162. [PMID: 34039486]; [DOI: 10.1016/j.jhep.2021.01.025]
26. Bacchi E, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, Zanolin E, Schena F, Bonora E, Moghetti P. Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial). *Hepatology.* 2013 Oct; **58(4)**: 1287-95. [PMID: 23504926]; [DOI: 10.1002/hep.26393]
27. Kim D, Konyn P, Cholankeril G, Ahmed A. Physical Activity Is Associated With Nonalcoholic Fatty Liver Disease and Significant Fibrosis Measured by FibroScan. *Clin Gastroenterol Hepatol.* 2021; **29**: S1542-3565(21)00693-5. 678.
28. Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M, Ma M, Abbraldes JG, Paterson I, Haykowsky MJ, Tandon P. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. *Clin Gastroenterol Hepatol.* 2014 ; **12**: 1920-6.e2. [PMID: 24768811]; [DOI: 10.1016/j.cgh.2014.04.016]
29. Román E, García-Galcerán C, Torrades T, Herrera S, Marín A, Doñate M, Alvarado-Tapias E, Malouf J, Nácher L, Serra-Grima R, Guarner C, Cordoba J, Soriano G. Effects of an Exercise Programme on Functional Capacity, Body Composition and Risk of Falls in Patients with Cirrhosis: A Randomized Clinical Trial. *PLoS One.* 2016 ; **11(3)**: e0151652. [PMID: 27011355]; [PMCID: PMC4807034]; [DOI: 10.1371/journal.pone.0151652]
30. Macías-Rodríguez RU, Ilarraza-Lomeli H, Ruiz-Margáin A, Ponce-de-León-Rosales S, Vargas-Vorácková F, García-Flores O, Torre A, Duarte-Rojo A. Changes in Hepatic Venous Pressure Gradient Induced by Physical Exercise in Cirrhosis: Results of a Pilot Randomized Open Clinical Trial. *Clin Transl Gastroenterol.* 2016; **7**: e180. [PMID: 27415618]; [PMCID: PMC5543482]; [DOI: 10.1038/ctg.2016.38]
31. Berzigotti A, Albillos A, Villanueva C, Genescá J, Ardevol A, Agustín S, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. *Hepatology.* 2017; **65(4)**: 1293-305. [PMID: 27997989]; [DOI: 10.1002/hep.28992]
32. Morkane CM, Kearney O, Bruce DA, Melikian CN, Martin DS. An Outpatient Hospital-based Exercise Training Program for Patients with Cirrhotic Liver Disease Awaiting Transplantation: A Feasibility Trial. *Transplantation.* 2020; **104**: 97-103. [PMID: 31205265]; [DOI: 10.1097/TP.0000000000002803]