

Reduced peripheral and inspiratory muscle endurance in patients with liver cirrhosis: a cross-sectional study

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ABSTRACT – Background – Liver cirrhosis (LC) causes several musculoskeletal changes. **Objective** – To test the hypothesis that the peripheral and inspiratory muscle endurance are reduced in patients with liver cirrhosis. **Methods** – Twenty-one patients with LC (LC group; 61±14 years) and 18 age-matched subjects (control group; 56±17 years) had accepted to participate in this cross-sectional observational study. To assess peripheral muscle endurance, all volunteers performed a rhythmic handgrip exercise at 45% of their maximum voluntary contraction. A metronome was used to control the contraction-relaxation cycles at 60/min. The inspiratory muscle endurance was assessed using PowerBreath®. Participants underwent inspiratory muscle exercise at 60% of their maximal inspiratory muscle strength. The time until failure characterized the muscle endurance for both handgrip and inspiratory muscle exercises. Additionally, the quality of life of the participants was assessed. **Results** – The muscle endurance was lower in the LC group when compared to the control group for both handgrip (67 vs 130 s, $P<0.001$) and inspiratory muscle exercises (40 vs 114 s, $P<0.001$). The peripheral muscle endurance was directly correlated with the total quality of life score ($r=0.439$, $P=0.01$) and to the following domains: fatigue ($r=0.378$, $P=0.030$), activity ($r=0.583$, $P=0.001$), systemic symptoms ($r=0.316$, $P=0.073$) and preoccupation ($r=0.370$, $P=0.034$). The inspiratory muscle endurance was inversely correlated with the total quality of life score ($r=0.573$, $P=0.001$) and the following domains: fatigue ($r=0.503$, $P=0.002$), activity ($r=0.464$, $P=0.004$), systemic symptoms ($r=0.472$, $P=0.004$), abdominal symptoms ($r=0.461$, $P=0.005$), emotional function ($r=0.387$, $P=0.02$) and preoccupation ($r=0.519$, $P=0.001$). **Conclusion** – Both peripheral and inspiratory muscle endurance were lower in LC patients when compared to the control group.

Keywords – Fatigue; quality of life; liver cirrhosis; physical endurance.

INTRODUCTION

The continuous long-term injury of hepatic parenchymatous cells coupled with the formation of fibrous tissues and nodules of regeneration leads to liver cirrhosis⁽¹⁾.

The patients with liver cirrhosis show a reduction in muscle mass due to several factors, the main one being protein-calorie malnutrition⁽²⁻⁴⁾. Another factor that generates the decrease in muscle mass is the reduction in anabolism and the increase in protein catabolism⁽⁵⁾.

These nutritional and catabolic effects on skeletal muscles occur in the whole body, in other words, the muscle functioning of patients with cirrhosis is impaired. Some studies showed that the maximum force of respiratory muscles, quadriceps and forearm muscles decrease as disease progress⁽⁶⁻¹⁰⁾. On the other hand, the peripheral and inspiratory muscle endurance in patients with liver cirrhosis are not fully understood. In addition, skeletal muscle endurance is important to daily-life activity. Thus, the structural and functional impairments described above could lead to a reduction in the qual-

ity of life. In fact, patients with cirrhosis have reduced quality of life in comparison to patients infected by hepatitis viruses⁽⁶⁾. In this regard, the most impaired domains were the functional capacity and limitations due to physical impairment⁽⁶⁾. Therefore, studies that addressed the effects of liver cirrhosis on the peripheral muscle endurance and the inspiratory muscle endurance, and its association with the quality of life are warranted.

Hence, the objective of this study is to evaluate both peripheral and respiratory muscle endurance in patients with liver cirrhosis. In addition, we assessed whether the skeletal muscle endurance would be associated with the quality of life of these patients.

METHODS

Participants and ethical approval

This is a cross-sectional observational study, which was conducted in the Cardiovascular Research Unit and Exercise Physiology of the University Hospital of the Federal University of Juiz de Fora.

Patients with liver cirrhosis were recruited from an outpatient

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clinic. A control group with individuals free from liver cirrhosis was also enrolled. Participants were older than 18 years and were not engaged in physical activities for at least three months prior enrollment. Patients with cirrhosis and encephalopathy at stage two, which was detected by a physician at the hepatology department, were excluded. Any participant that have presented cognitive impairment, cardiorespiratory abnormality or skeletal muscle impairment was also excluded.

The research protocol was approved by the Ethical Committee of the University Hospital of the Federal University of Juiz de Fora (no. 2.742.851). All the participants were made aware, both verbally and written, of the procedures and measures of the research protocol they would be submitted to and signed an informed consent before enrollment.

The MELD score, Child-Pugh's classification, the history of cirrhosis decompensation caused by portal hypertension (i.e. digestive hemorrhage, ascites or hepatic encephalopathy), alanine transaminase (ALT), aspartate transaminase (AST), gama-glutamyltransferase (GGT), bilirubin, albumin, international normalized ratio (INR), platelets and creatinine were obtained via patient records.

Quality of life

The quality of life was assessed using Chronic Liver Disease Questionnaire, which was validated to the Brazilian population (CLDQ-BR). The CLDQ-BR is a specific questionnaire to evaluate the quality of life of patients with chronic hepatic diseases. It consists of 29 items distributed in 6 domains: fatigue (questions 2, 4, 8, 11 and 13), activity (questions 7, 9 and 14), emotional function (questions 10, 12, 15, 16, 19, 20, 24 and 26), abdominal symptoms (questions 1, 5 and 17), systemic symptoms (questions 3, 6, 21, 23 and 27) and concern (questions 18, 22, 25, 28 and 29). The scores calculated for each domain range vary from 1 to 7. The score in each domain is obtained by the sum of the answers and divided by the number of questions related to the specific domain. And the total score of the CLDQ-BR is obtained by the sum of domains and divided by 6⁽¹¹⁾.

Cardiovascular and respiratory measurements

After a 10-minute rest period, we measured the systolic blood pressure (SBP), diastolic blood pressure (DBP) mean blood pressure (MBP), heart rate (HR), and oxygen peripheral saturation (SatO₂) in the sitting position. The blood pressure was measured by the oscillometric method using an automatic and non-invasive device (DX2022, Dixtal, Manaus, Brazil), in which the cuff was placed on the upper non-dominant limb of the volunteer. The HR was obtained by electrocardiogram using five cutaneous electrodes placed according to the standard lead of the multi-parametric monitor (DX2022, Dixtal, Manaus, Brazil)⁽¹²⁾. The SatO₂ was assessed by a peripheral sensor placed on the middle finger (DX2022, Dixtal, Manaus, Brazil). The respiratory frequency (f) was recorded observing the thoracic expansion of the participant at rest.

Peripheral muscle endurance

Firstly, the maximal peripheral muscle strength was assessed using a digital hand grip dynamometer (EMG System®, São Paulo, Brazil) and the signal was recorded by an analogic-digital acquisition system (Windaq Pro, DATAQ Instruments) at a frequency of 500 Hz. The participants underwent three attempts of maximal voluntary contraction (MVC) of both arms. This assessment was performed alternating the limbs and each measure was separated by a 2-minute interval. In accordance with the American Society

of Hand Therapists⁽¹³⁾, the participant was placed in sitting position, elbow flexed at 90°, forearm in the neutral position and wrist hyperextended at 0 to 30°. The MVC was determined by the average of the three attempts.

Then, the peripheral muscle endurance was assessed by the rhythmic handgrip exercise at 45% of the MVC with a duty cycle of 60 contraction-relaxation per minute, which was controlled by a metronome. The exercise was performed until the participant was no longer able to contract at 45% of the MVC during three consecutive contractions despite verbal encouragement. Then, the time (in seconds) until the last contraction performed at the target intensity was recorded and used to represent peripheral muscle endurance. The participants were not informed about the failure criteria of the test to avoid any potential external influence on the assessment. The volunteers remained sitting with elbows at 90° and had visual access to a monitor in order to identify the required force⁽¹⁴⁾. The volunteers remained 10 minutes at rest before and after the test.

Respiratory muscle endurance

The maximal respiratory muscle strength was evaluated by the maximal inspiratory pressure (PI_{max}) and the maximal expiratory pressure (PE_{max}) using a digital manovacuometer (MVD300 GlobalMed®, Porto Alegre, Brazil). The participants were placed in a sitting position, using a nasal clip and rigid plastic bucal with a 2 mm hole to release pressure caused by the mouth. For the PI_{max} assessment, the volunteer had to perform a complete expiration (to the residual volume) followed by a maximal inspiratory effort (to total lung capacity), which was maintained for at least 1 second. For the PE_{max} assessment, it was requested that the participants perform a complete inspiration (to the maximal pulmonary capacity) followed by a maximal expiratory effort (total lung capacity), which, was maintained for at least 1 second. Three to five reproducible measures were performed (showing 10% differences between the values) and the higher value was recorded⁽¹⁵⁾.

The inspiratory muscle endurance was assessed using the PowerBreathe Plus® and nasal clip. The volunteer had to mouth-breathe at 18 respiratory incursions per minute (IRPM), which was controlled by a metronome, till exhaustion. The inspiratory muscle endurance test was performed at 60% PI_{max}. The test was interrupted when the participants were no longer able to keep the 18 IRPM or when they asked to stop it. The time (in seconds) recorded between the beginning and the interruption of the test characterized the inspiratory muscle endurance^(16,17).

Experimental protocol

The individual who agreed to participate in the research signed the informed consent form, answered the anamnesis and the CLDQ-BR quality of life questionnaire, and then underwent anthropometric assessment. After 10 minutes in the sitting position, HR and resting blood pressure were collected.

Then, the evaluation of the maximum peripheral strength was performed to identify the MVC value. After 10 minutes of rest, the volunteer performed the peripheral muscle endurance test at 45% of MVC, as previously described.

After 10 minutes of rest, respiratory muscle strength was assessed, which consisted of assessing PI_{max} and PE_{max} using manovacuometry. After 5 minutes at rest, the inspiratory muscle endurance test was performed at 60% of PI_{max}, as previously described.

Statistics analysis

The data is presented as mean ± standard deviation (SD) or absolute frequency (n). The Shapiro-Wilk test was used to analyze the data distribution. The categories variables were subjected to Pearson's chi-squared or Fisher's exact test when appropriate. The comparison between groups for continuous variables was performed using the test *t* by Student for independent samples. The effect size was analysed by the "d" of Cohen considering the following cutoff points: insignificant (<0.2), small (from 0.2 to 0.5), medium (from 0.5 to 0.8) and large (>0.8)^(18,19). The association between the muscle endurance and the quality of life was analyzed using Pearson's correlation coefficient. The statistical significance was set at $P \leq 0.05$. All statistical tests were performed using the statistical package for social sciences (IBMSPPSS) version 22.0.

RESULTS

Forty participants accepted to participate in this study: 22 patients with liver cirrhosis and 18 subjects free of cirrhosis composing the control group. However, four volunteers (patients with liver cirrhosis: n=3; control group: n=1) were excluded because they did not perform the experimental protocol appropriately. Then, the data from 36 participants were considered in the analysis (patients with liver cirrhosis: n=19; control group: n=17). Three participants (patients with liver cirrhosis =2; control group=1) were excluded from the peripheral muscle endurance evaluation for not being able to execute the proposed protocol. Hence, 33 participants executed the peripheral muscle endurance evaluation, making it 17 from patients with liver cirrhosis and 16 from control group (FIGURE 1).

Participants characteristics

The characteristics and the quality of life of both groups are shown in TABLE 1. The groups were similar in regards to sex, age, weight, height, BMI, waist circumference, SBP, DBP, MBP, HR, *f* and SatO₂ at rest. However, the patients with liver cirrhosis showed a lower circumference of both left and right arms when compared to the control group. As compared to the control group, the patients with liver cirrhosis showed lower values of peripheral muscle strength in both arms, maximal expiratory force, total quality of life and in the following domains: fatigue, activity, abdominal symptoms, systemic symptoms and preoccupation. On the other hand, both groups presented similar results when it comes to maximal inspiratory force and the domain of emotional function of the quality of life (TABLE 1).

TABLE 1. Demographic, antropometric, hemodynamic characteristics at rest and quality of life.

Variable	LCG (n=19)	CG (n=17)	P	D Cohen
Sex (male)	16	11	0.26	-
Age (years)	61±14	56±17	0.27	-
Weight (kg)	82.07±14.55	84.19±12.64	0.65	0.16
Height (cm)	172±9	169±11	0.50	-0.23
BMI (kg/m ²)	28.12±6.34	29.33±3.82	0.50	0.24
Right arm Circumference (cm)	28.6±4.9	31.5±2.7	0.04	0.75
Left arm circumference (cm)	28.2±5.1	31.0±2.6	0.05	0.73
Waist circumference (cm)	97.6±17.7	92.2±11.6	0.29	-0.37
SBP (mmHg)	129±14	131±13	0.76	0.10
DBP (mmHg)	74±7	76±9	0.41	0.28
MBP (mmHg)	92±9	94±9	0.52	0.22
HR (bpm)	70±12	77±10	0.08	0.60
<i>f</i> (irpm)	17±2	16±1	0.19	-0.45
SatO ₂ (%)	98±2	97±2	0.45	-0.26
MVC right arm (kgf)	37.87±9.40	48.07±8.63	0.00	1.05
MVC left arm (kgf)	36.37±12.73	45.15±8.38	0.02	0.83
PImax (cmH ₂ O)	64.26±20.02	75.71±21.34	0.11	0.55
% PImax predicted	63.33±18.78	74.84±17.77	0.07	0.63
PEmax (cmH ₂ O)	74.63±27.73	95.53±20.62	0.03	0.78
% PEmax predicted	69.02±25.80	89.20±18.69	0.01	0.91
Quality of life				
Fatigue domain	3.73±1.29	5.11±1.19	0.00	1.11
Activity domain	5.26±0.89	6.31±1.00	0.00	1.11
Emotional function domain	4.10±1.35	4.91±1.27	0.07	0.62
Abdominal symptoms domain	4.81±1.54	6.63±0.81	0.00	1.55
Systemics symptoms domain	4.32±1.45	5.85±1.21	0.00	1.15
Worry domain	4.36±1.65	6.69±0.68	0.00	2.0
Total quality of life	4.43±1.01	5.92±0.82	0.00	1.63

Values: mean ± standard deviation of the mean; LCG: liver cirrhosis group; CG: control group; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; HR: heart rate; *f*: respiratory frequency; SatO₂: peripheral oxygen saturation; MVC: maximal voluntary contraction; PImax: inspiratory muscle strength; PEmax: expiratory muscle strength.

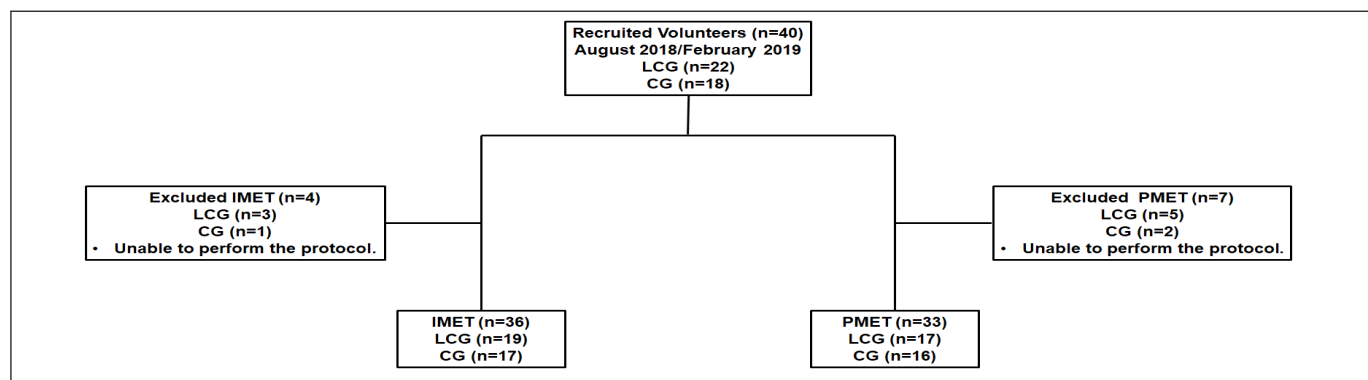


FIGURE 1. Study flowchart. LCG: liver cirrhosis group; CG: control group; PMET: Peripheral Muscular Endurance Test; IMET: Inspiratory Muscular Endurance Test.

The etiologies of cirrhosis were alcoholic (37%), non-alcoholic steatohepatitis (31%), autoimmune hepatitis (11%), hepatitis C (11%), hepatitis B (5%) and Budd Chiari syndrome (5%). In regard to cirrhosis stratification, 68% of patients were classified as child A, 32% as child B and, altogether, presented MELD 11 ± 3 . Thirty-seven percent of patients developed ascites, 16% esophageal varicose and 5% grade 1 encephalopathy. The patients presented albumin 3.62 ± 0.55 g/dL, total bilirubin 1.01 ± 0.50 mg/dL, indirect bilirubin 0.44 ± 0.16 mg/dL, RNI 1.23 ± 0.25 , gamma-glutamyltransferase 186.67 ± 274.75 U/L, oxaloacetic transaminase 44.79 ± 32.75 U/L, glutamic pyruvic transaminase 31.32 ± 19.01 U/L, creatinine 1.28 ± 1.48 mg/dL.

Muscle endurance

The peripheral muscle endurance and the inspiratory muscle endurance were lower in the patients with liver cirrhosis when compared to the control group (FIGURE 2). The effect size of these comparisons was classified as large.

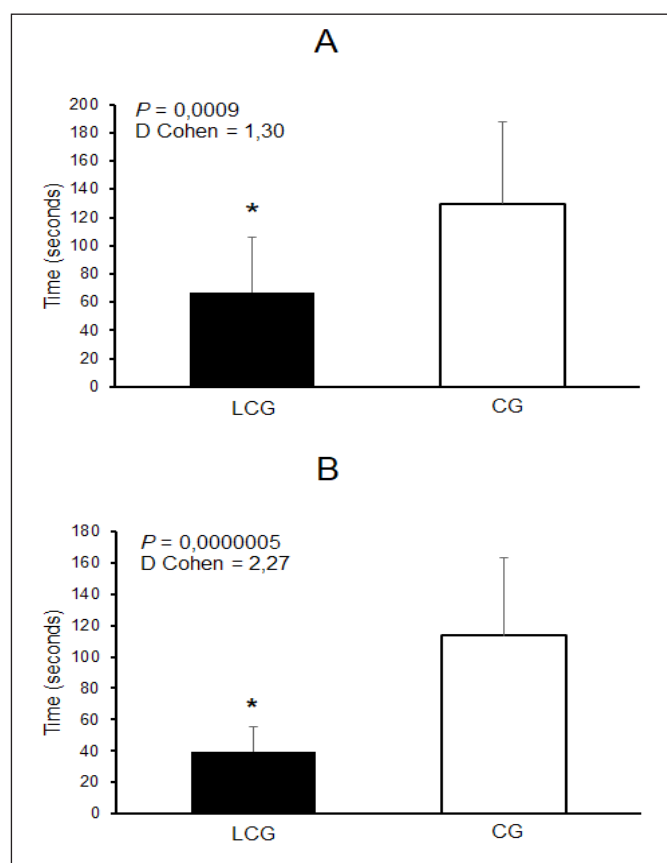


FIGURE 2. Between-group comparisons in regards to of peripheral muscle endurance (A) and inspiratory muscle endurance (B).

LCG: liver cirrhosis group; CG: control group; $*=P \leq 0.05$ vs CG; D Cohen = 1.30; 2.27, respectively; LCG: black bar; CG: white bar.

A direct correlation was observed between the peripheral muscle endurance and the total quality of life. In addition, it was observed a direct correlation between the peripheral muscle endurance and the domains fatigue, activity, emotional issues and preoccupation of CLDQ-BR, but not for the domains of abdominal and systemic symptoms (FIGURE 3).

The inspiratory muscle endurance was directly correlated to the total quality of life. In addition, we observed a direct correlation between the peripheral muscle endurance and the following domains: fatigue, activity, emotional issues, abdominal symptoms, systemic symptoms and preoccupation (FIGURE 4).

Furthermore, the peripheral muscle endurance was directly correlated to the inspiratory muscle endurance ($P=0.001$ and $r=0.571$).

DISCUSSION

The novelty of this study is that patients with liver cirrhosis showed lower peripheral muscle endurance and inspiratory muscle endurance when compared to individuals who do not present such disease. In addition, we have observed that there is an association between the quality of life of the participants and both peripheral and inspiratory muscle endurance.

The reduction of the maximal force of the peripheral musculature was observed in both dominant and non-dominant forearms in patients with liver cirrhosis. In agreement with our results, a previous study has reported a 40% reduction in the force of left and right hands in patients with liver cirrhosis⁽¹⁰⁾.

Another study evaluated the handgrip strength in 129 patients with cirrhosis. In this research we have also observed a reduction in peripheral muscle strength when compared to the predicted values, besides having not reported any association between the reduction in peripheral muscle strength and the evolution of the disease according to Child-Pugh's classification⁽²⁰⁾.

The expiratory muscle strength was lower in the patients with liver cirrhosis in comparison to the control group and there was no significant difference in inspiratory muscle strength between the two groups.

On the other hand, both groups presented similar results when it comes to maximal inspiratory force and the domain of emotional function of the quality of life^(6-8,21).

In the present study, the fact that only the respiratory muscle strength is reduced for being associated with the classification/evolution of the disease once 68% of the patients were classified as child A demonstrates that half of the liver cirrhosis samples do not find themselves in its severe stage.

The maximal muscle strength of respiratory muscles and the functional capacity were investigated in 35 patients who were treated in an outpatient clinic for hepatic transplant in the South of Brazil. Nineteen of them were classified as child B and 16 as child C. The authors showed that the score of Child-Pugh's classification was negatively correlated to the PImax. In addition, a significant association between the PImax and the distance walked in the 6-minute walk test was observed only in child B patients. These results suggest that respiratory muscle strength deteriorates as cirrhosis progress⁽⁸⁾.

The loss of skeletal muscle mass is prevalent in patients with cirrhosis and it can predict physical deconditioning, physical dependence and mortality^(22,23). Our results showed a lower peripheral and inspiratory muscle endurance in liver cirrhosis patients, which can be associated with the sarcopenia⁽²³⁾ and physical inactivity. As the literature suggests, we can observe a positive correlation when verifying the peripheral muscle endurance and the activity and fatigue domains.

The fatigue of the peripheral and respiratory muscles may occur during physical exercises and during several situations of daily life. This effect may impair the daily tasks of the patients with cirrhosis causing physical and emotional dependence and, then, reducing

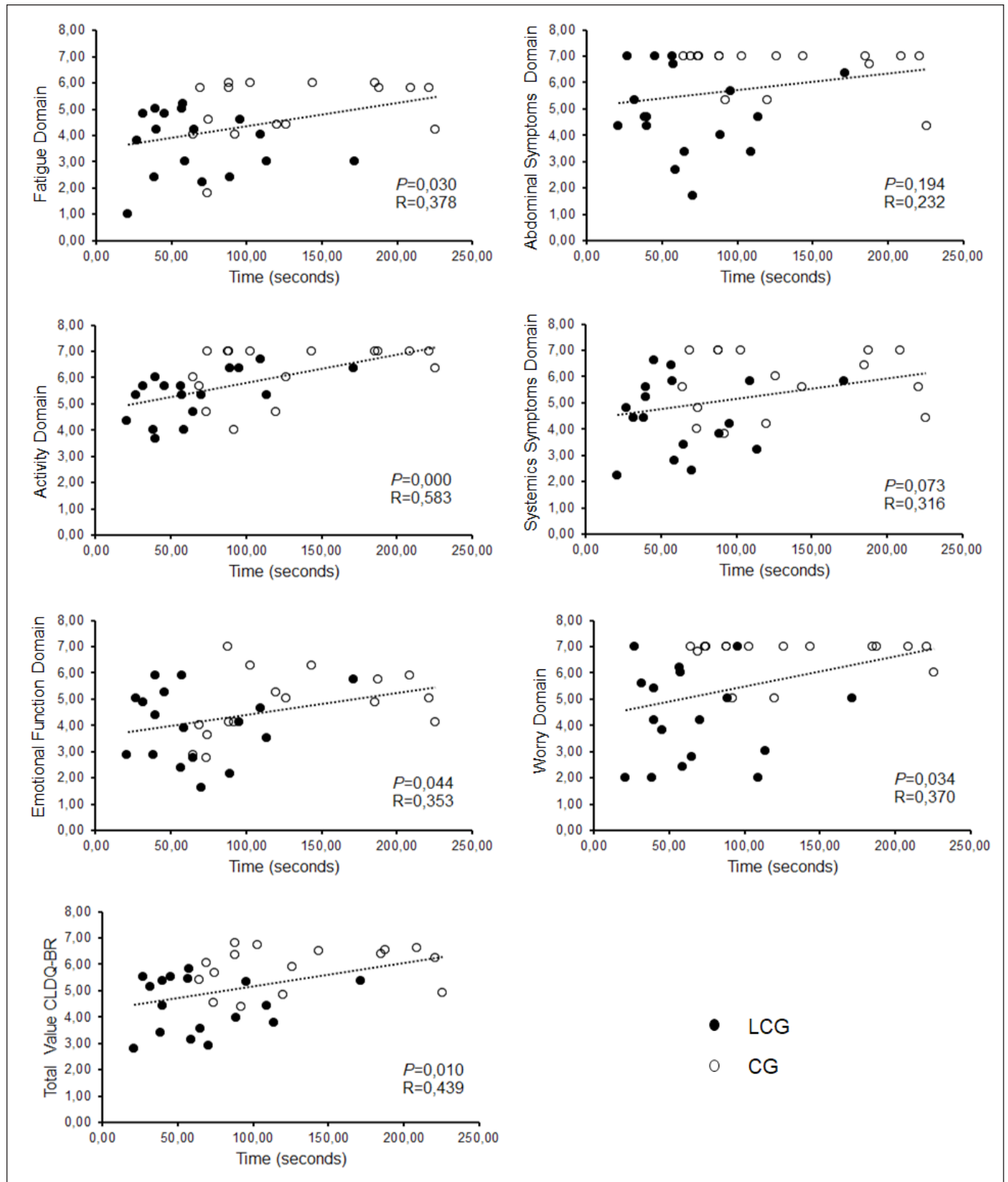


FIGURE 3. Correlation between the peripheral muscle endurance test, and quality of life and its domains.
 CLDQ-BR: Chronic Liver Disease Questionnaire – Brazil; LCG: liver cirrhosis group; CG: control group.

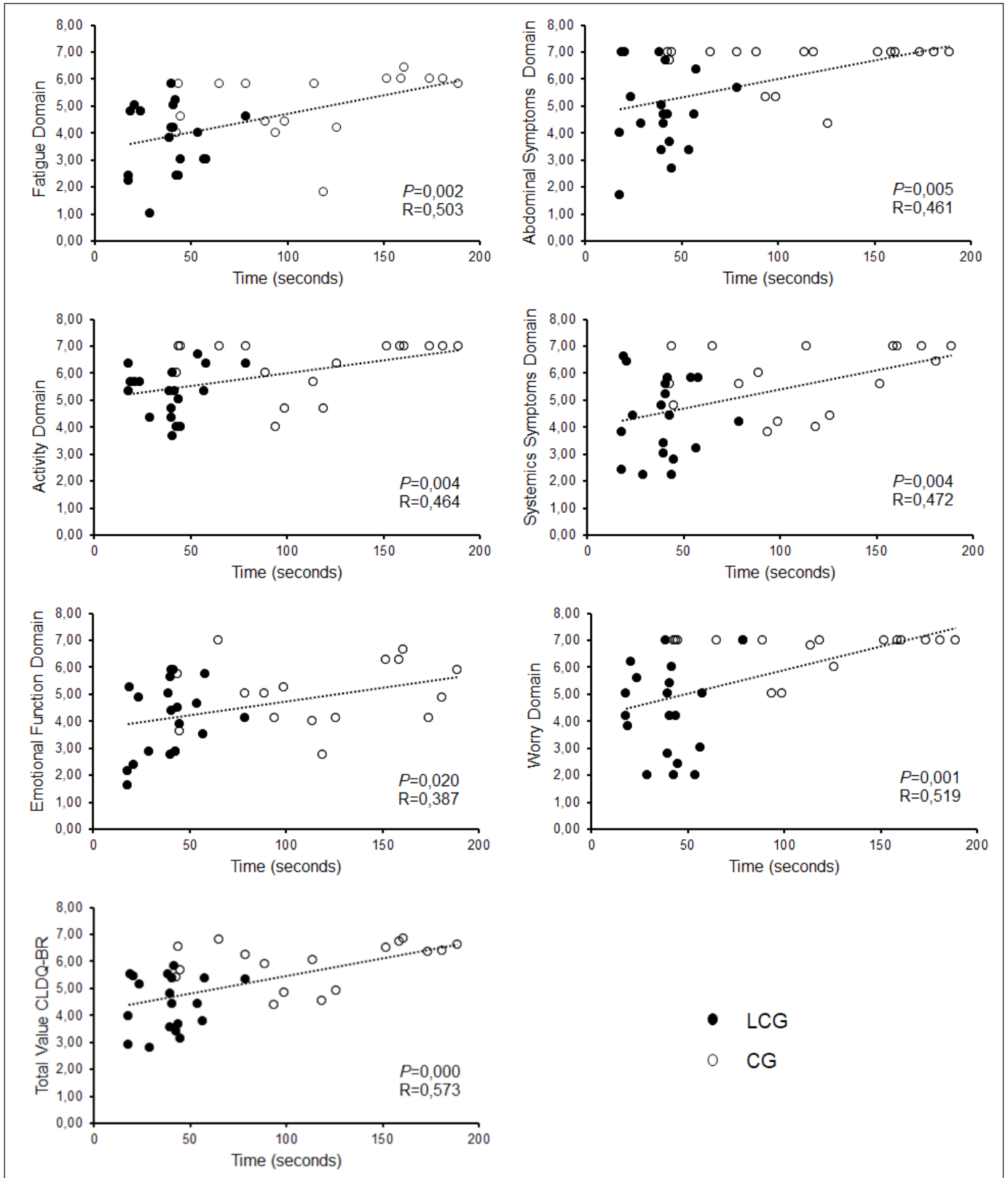


FIGURE 4. Correlation between the inspiratory muscle endurance test, and quality of life and its domains.
CLDQ-BR: Chronic Liver Disease Questionnaire – Brazil; LCG: liver cirrhosis group; CG: control group.

their quality of life^(24,25). In this regard, we observed a reduction in the quality of life of patients with cirrhosis, mainly in terms of fatigue, activities, abdominal symptoms, systemic symptoms and preoccupation.

Assessing the quality of life and correlating it with laboratory tests of 472 patients with liver cancer, 59% of the volunteers had liver cirrhosis. There was a correlation between high levels of bilirubin and a worse quality of life in these patients, that is, the lower the level of bilirubin, INR and ALP, the better the quality of life in the evaluated volunteers⁽²⁶⁾.

Muscle endurance is important to daily tasks such as carry a heavy bag or climb up stairs. Impaired peripheral and inspiratory muscle endurance leads to a reduction in physical activity and health-related quality of life, which can worsen these patients' conditions both socially and psychologically.

This study presents a limitation. The sarcopenia was not assessed due to the lack of expensive exams such as computerized tomography or magnetic resonance imaging in our laboratory. However, the arm circumference and the handgrip maximal force were lower in patients with cirrhosis, which suggest that these patients present both loss of muscle mass and functioning.

CONCLUSION

In conclusion, the patients with liver cirrhosis showed lower muscle endurance in both handgrip and inspiratory musculatures in comparison with subjects free from cirrhosis. In addition, respiratory and peripheral muscle endurance were directly associated with quality of life.

Authors' contribution

Corrêa FCCR: data collect, research execution, text writing and statistical analysis. Mira PAC, Pace FHL, Laterza MC: text revision. Trevizan PF, Martinez DG: guidance and text revision.

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RESUMO – Contexto – A cirrose hepática (CH) causa várias alterações musculoesqueléticas. **Objetivo** – Testar a hipótese de que as resistências dos músculos periféricos e inspiratórios estão reduzidas em pacientes com CH. **Métodos** – Vinte e um pacientes com CH (grupo CH; 61±14 anos) e 18 indivíduos pareados por idade (grupo controle; 56±17 anos) aceitaram participar deste estudo observacional transversal. Para avaliar a resistência muscular periférica, todos os voluntários realizaram um exercício de prensão manual rítmica a 45% de sua contração voluntária máxima. Um metrônomo foi usado para controlar os ciclos de contração-relaxamento a 60/min. A resistência muscular inspiratória foi avaliada com o PowerBreath®. Os participantes foram submetidos a exercícios musculares inspiratórios a 60% de sua força muscular inspiratória máxima. O tempo até a falha caracterizou a resistência muscular para os exercícios de prensão manual e de músculos inspiratórios. Além disso, foi avaliada a qualidade de vida dos participantes.

Resultados – A resistência muscular foi menor no grupo CH quando comparada ao grupo controle tanto para os exercícios de prensão manual (67 vs 130 s, $P<0,001$) quanto para os músculos inspiratórios (40 vs 114 s, $P<0,001$). A resistência muscular periférica foi diretamente correlacionada com o escore total de qualidade de vida ($r=0,439$, $P=0,01$) e com os seguintes domínios: fadiga ($r=0,030$, $P=0,378$), atividade ($r=0,378$ e $P=0,030$), sintomas sistêmicos ($r=0,316$, $P=0,073$) e preocupação ($r=0,370$, $P=0,034$). A resistência muscular inspiratória foi inversamente correlacionada com o escore total de qualidade de vida ($r=0,573$, $P=0,001$) e com os seguintes domínios: fadiga ($r=0,503$, $P=0,002$), atividade ($r=0,464$, $P=0,004$), sintomas sistêmicos ($r=0,472$, $P=0,004$), sintomas abdominais ($r=0,461$, $P=0,005$), função emocional ($r=0,387$, $P=0,02$) e preocupação ($r=0,519$, $P=0,001$).

Conclusão – As resistências musculares periférica e inspiratória foram menores nos pacientes com CH quando comparados ao grupo controle.

Palavras-chave – Fadiga; qualidade de vida; cirrose hepática; resistência.

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