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# Capacity of exercise and survival in patients with cirrhosis with and without hepatopulmonary syndrome after liver transplantation

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**ABSTRACT** – **Background** – Hepatopulmonary syndrome (HPS) is a complication associated with cirrhosis that may contribute to worsening exercise capacity and reduced survival after liver transplantation (LT). **Objective** – To evaluate exercise capacity, complications and survival after LT in patients with cirrhosis and HPS and to compare these results with the results of patients with cirrhosis without HPS. **Methods** – A prospective cohort study, consisting initially of 178 patients, of whom 90 underwent LT (42 with HPS and 48 without HPS). A previous evaluation consisted of the six-minute walk test (6MWT), an exercise test and manovacuometry. Those who underwent LT were evaluated for the mechanical ventilation time (MV), non-invasive ventilation (NIV) use, and survival two years after the procedure. In the statistical analysis, we used the Kolmogorov-Smirnov test, Student's t-test, the linear association square test, and the Kaplan-Meier survival curve. The data were analyzed with the SPSS 16.00 program and considered significant at $P<0.05$. **Results** – The HPS group demonstrated a lower peak of oxygen consumption ($VO_2$peak) (14.2±2.3 vs 17.6±2.6) $P<0.001$ and a shorter distance walked on the 6MWT (340.8±50.9 vs 416.5±91.4) $P<0.001$ before LT compared with the non-HPS group. The transplanted patients with HPS remained longer hours in MV (19.5±4.3 vs 12.5±3.3) $P=0.02$, required more NIV (12 vs 2) $P=0.01$, and had lower survival two years after the procedure ($P=0.01$) compared with the transplanted patients without HPS. **Conclusion** – Patients with HPS had worse exercise capacity before LT, more complications and shorter survival after this procedure than patients without HPS.

**HEADINGS** – Liver cirrhosis. Hepatopulmonary syndrome. Liver transplantation.

## INTRODUCTION

Hepatic cirrhosis is characterized by diffuse replacement of the normal hepatic structure by abnormal nodules surrounded by fibrosis, and it is present in the final stage of a series of liver pathological processes arising from various causes[1]. Metabolic changes associated with malnutrition in patients, who lose a large amount of muscle mass and thus present with alterations in functionality as well as physical inactivity, are among some of the main complications of these patients; the association of all these factors has a negative influence on the activities of daily living and the quality of life of this population[2-5].

The treatment of patients with cirrhosis is complex and should be further expanded, as it currently demonstrates a relatively low survival prospect. Liver transplantation (LT) has been demonstrated to provide better survival in these patients and low treatment expenditure[6-8]. However, it is important to note that many candidates spend long periods on waiting lists for LT, and this situation favors the appearance of new complications, which can worsen functionality and decrease survival.

Hepatopulmonary syndrome (HPS), which is defined by a triad involving hepatic disease and/or portal hypertension, intrapulmonary vascular dilations (IPVDs), and arterial oxygenation abnormalities (partial oxygen pressure ($PaO_2$) less than 70 millimeters of mercury (mmHg) or alveolar-arterial oxygen gradient ($P(Aa)O_2$) greater than 20 mmHg in ambient air), is one of the complications that may arise as a result of liver disease, demonstrating a prevalence of 16% to 24% according to previous studies in this population[9-15].

Considering the direct relationship between physical condition and the supply of oxygen to tissues, we believe that changes caused by HPS in gas exchange may play important roles in the intolerance to exercise in this population. Thus, severe physical inactivity is expected in patients with cirrhosis and HPS as well as, consequently, worse functional condition at the time of LT these outcomes may compromise the immediate postoperative period and may reduce the patient's survival.

Thus, the objective of this study was to evaluate the functional status, exercise capacity and respiratory muscle strength of patients with cirrhosis with a diagnosis of HPS before LT and to compare these results with the results of patients with cirrhosis without HPS. After liver transplantation, these two groups were compared regarding the time of mechanical ventilation (MV), the need to use noninvasive ventilation (NIV), the length of hospital stay and the mortality after thirty days and two years.

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## METHODS

This study contains a prospective cohort with a convenience sample, consisting of 90 patients from a single center who were diagnosed with cirrhosis due to hepatitis C virus (HCV) or alcohol and who underwent LT (42 with HPS and 48 without HPS). All of the patients were part of a group of approximately 500 individuals who were monitored by the Liver Transplant Clinic of the Santa Casa de Misericordia Hospital Complex (*Ambulatório de Transplante Hepático do Complexo Hospitalar Santa Casa de Misericórdia*), Porto Alegre, Rio Grande do Sul State, Brazil, and the study was conducted between 2014 and 2018. The project was approved by the Research Ethics of the institution in question under number 331.068

For inclusion in the study, all of the patients signed the informed consent form, performed a physical evaluation composed of the six-minute walk test (6MWT), the ergometric test to identify the peak oxygen consumption ($VO_2$peak), and manovacuometry to verify the maximum respiratory pressures. All of these evaluations were repeated during the time the patients were undergoing outpatient follow-up so that their last evaluation was at least 30 days before LT. Individuals who underwent LT were followed for a period of two years.

The exclusion criteria were as follows: last physical therapy evaluation more than 30 days before LT; a significant previous obstructive ventilatory deficit, defined as a Tiffeneau index of less than 0.70 with a forced expiratory volume in one second (FEV1) lower than 80; significant predictive ventilatory deficit, defined by a forced vital capacity (FVC) of less than 70% of the predicted value; the presence of an intracardiac shunt; and cognitive and/or orthopedic alterations that made it difficult to perform the proposed tests. The project was approved by the Research Ethics Committee of the hospital complex under opinion number 331.068.

A diagnosis of HPS was made according to pre-established criteria. Patients with cirrhosis underwent contrast echocardiography, where aerated saline solution was injected through the antecubital vein into the circulation. The microbubbles resulting from this process have diameters of 60 to 90 μm, which are larger than those in the normal capillary bed, which have diameters of 8 to 15 μm and thus will opacify only the right heart chambers. However, with the loss of the anatomic barrier resulting from the presence of dilation of the intrapulmonary capillary bed, the microbubbles can reach the left chambers between 3 and 6 cardiac cycles after their rightward appearance. Associated with contrast echocardiography, the gasometric parameters, especially the alveolar-arterial oxygen gradient ($P(A\text{-}a)O_2$), were evaluated since the isolated analysis of the arterial oxygen pressure ($PaO_2$) may underestimate the true degree of hypoxemia. We defined a $P(A\text{-}a)O_2$ greater than 20 mmHg in our study due to its good accuracy demonstrated in previous studies[14,15].

The 6MWT was performed according to the norms of the American Thoracic Society. The variables including respiratory rate, heart rate, peripheral oxygen saturation, and Borg scale for dyspnea and fatigue in the lower limbs were verified before and after the test, and the distance covered was recorded at the end of the test[16].

Respiratory muscle strength was assessed according to the pulmonary function test guidelines of the Brazilian Society of Pneumology and Tisiology[17]. As many as five maneuvers were performed to measure the maximum inspiratory pressure (MIP) and as many as five maneuvers to measure the maximum expiratory pressure (MEP), thus obtaining at least three acceptable maneuvers, that is, that the values did not differ by more than 10%. We then recorded the highest pressure in centimeters of water (cmH2O).

For the evaluation of cardiopulmonary capacity, a treadmill test was used via the modified Bruce protocol with gas exchange analysis, according to the American College of Sports Medicine[18]. $VO_2$peak (mL/kg/min) was used as an aerobic capacity index and was considered the highest value in a given minute during the protocol used. Only the tests in which the patients reached the anaerobic threshold were considered in the analysis to guarantee that all patients had reached a submaximal level of exercise.

Statistical analysis was performed using the Statistical Package for Social Sciences software, version 16.0. To verify the homogeneity of the sample, the Kolmogorov-Smirnov test was used; for the comparison of continuous variables, Student's *t*-test was used; and for the comparison of categorical variables, the chi-square test and linear association were used. A Kaplan-Meier survival curve was used for survival analysis in both groups, and Cox regression was used for analysis of the independent predictors. $P<0.05$ was considered significant. For the multivariate analysis, we considered only the variables that demonstrated $P<0.2$.

## RESULTS

TABLE 1 shows the clinical and anthropometric characteristics of the population. There was no difference between the groups regarding sex, the etiology of cirrhosis and the model for end-stage liver disease (MELD). Patients with cirrhosis diagnosed with HPS demonstrated lower $PaO_2$ and higher $P(A\text{-}a)O_2$ levels, walked a shorter distance in the 6MWT, and had a lower $VO_2$peak level and respiratory muscle strength compared with patients without HPS. The number of deaths after LT was significantly higher in patients with HPS than that in patients without HPS.

**TABLE 1.** Baseline characteristics of the sample.

| Variable | HPS+(42) | HPS- (48) |
|---|---|---|
| Age (years) | 61.2±6 | 59.2±7 |
| BMI | 24.8±1.5 | 26.5±6.6 |
| Sex | | |
| Male (n) | 23 | 32 |
| Female (n) | 19 | 16 |
| Cirrhosis Etiology | | |
| Alcohol (n) | 17 | 14 |
| HVC (n) | 25 | 34 |
| MELD | 18.4±0.6 | 18.6±3.2 |
| 6MWT (meters) | 334±19.2 | 392±57.2** |
| $VO_2$peak (ml/kg) | 14.9±1.6 | 16.8±2.6** |
| MIP (mmHg) | -47.8±6.8 | -66.6±8.0** |
| MEP (mmHg) | 58.1±5.3 | 70.8±6.1** |
| $PaO_2$ (mmHg) | 68.2±6.3 | 91.5±3.1** |
| $P(A\text{-}a)O_2$ (mmHg) | 24.2±1.6 | 11.3±1.5** |
| Number of deaths | 11 | 6* |

HPS+: with hepatopulmonary syndrome; HPS-: without hepatopulmonary syndrome; BMI: body mass index; HVC: hepatitis virus C; MELD: Model for End-Stage Liver Disease; 6MWT: Six-minute walk test; $VO_2$peak: peak oxygen consumption; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; $PaO_2$: Oxygen blood pressure; $P(A\text{-}a)O_2$: arterial alveolar oxygen gradient. *$P<0.05$. **$P<0.001$.

TABLE 2 shows the variables related to LT, ventilatory support and length of hospital stay. We did not find statistically significant differences in relation to the time of ischemia of the organ to be transplanted, time of surgery or mortality in the period of 30 days, but the patients in the HPS group stayed longer hours in MV (19.5±4.3 vs 12.5±3.3) *P*=0.02, had more days hospitalized in the intensive care unit (ICU) (6.7±2.1 vs 4.6±1.5) *P*=0.02, had more hospital stay days (24.1±4.3 vs 20.2±3.9) *P*=0.01, and required more NIV (12 vs 2) *P*=0.01 than the patients in the non-HPS group.

**TABLE 2.** Characteristics of liver transplant, ventilatory support, and hospitalization.

| Variable | | |
|---|---|---|
| Operative time (hours) | 4.2±1.2 | 4.5±1.0 |
| Organ ischemia (hours) | 6.5±2.1 | 6.3±2.5 |
| MV (hours) | 19.5±4.3 | 12.5±3.3* |
| ICU (days) | 6.7±2.1 | 4.6±1.5* |
| Hospital stay (days) | 24.1±4.3 | 20.2±3.9** |
| Use of NIV (n) | 12 | 2** |
| Deaths in thirty days | 2 | 2 |

HPS+: with hepatopulmonary syndrome; HPS-: without hepatopulmonary syndrome; MV: mechanical ventilation; ICU: intensive care unit; NIV: noninvasive ventilation. *$P$=0.02. **$P$=0.001.

In FIGURE 1, we present the Kaplan-Meier survival curve. The cirrhosis group without a diagnosis of HPS demonstrated higher survival in a period of two years than the cirrhosis group with a diagnosis of HPS (85% vs 75%), (*P*=0.01).

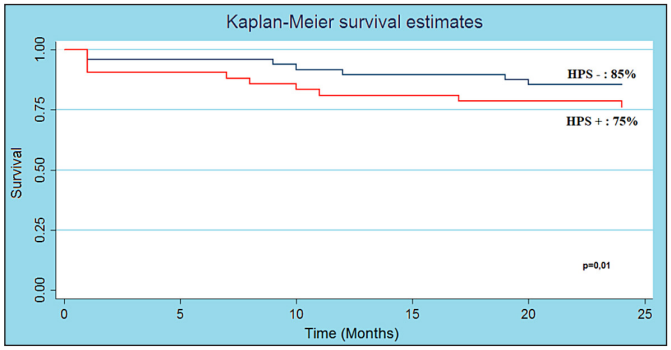


**FIGURE 1.** Survival after two years in patients with cirrhosis with (HPS+) and without hepatopulmonary syndrome (HPS-).

In the multivariate analysis (TABLE 3) adjusted for age, etiology, MELD, 6MWT, $VO_2$peak, MEP and MIP, we selected those variables that presented *P*<0.02 in the Cox univariate model, in which the 6MWT, $VO_2$peak and MIP remained independent predictors of mortality in the sample studied. There was 17% greater survival with the increase in the distance covered in the 6MWT (HR=0.83, CI95% =0.73–0.94, *P*=0.003); a good $VO_2$peak increased survival by up to 30% (HR=0.70, CI95% =0.57–0.82, *P*=0.001), and a higher MIP increased patient survival by up to 15% (HR=0.85, CI95% =0.75–0.92, *P*=0.002).

**TABLE 3.** Univariate and multivariate analyses of the variables under study.

| Variable | Non-adjustedanalysis | | Adjustedanalysis | |
|---|---|---|---|---|
| | HR (95%CI) | *P*-value | HR (95%CI) | *P*-value |
| Age | 1.05 (0.97–1.14) | **0.182** | 1.02 (0.91–1.14) | 0.742 |
| Sex | | | | |
| Female | 1.0 | | | |
| Male | 0.6 (0.26–1.76) | 0.426 | | |
| HPS | | 0.02 | | |
| No | 1.0 | | | |
| Yes | 1.74 (0.66–4.57) | | | |
| Diagnosis | | | | |
| Alcohol | 1.0 | | 1.0 | |
| VHC | 0.25 (0.09–0.68) | 0.007 | 2.19 (0.22–21.7) | 0.502 |
| MELD | 1.33 (1.11–1.60) | 0.02 | 1.22 (0.81–1.6) | 0.251 |
| 6MWT | 0.83 (0.77–0.91) | <0.01 | 0.80 (0.72–0.96) | 0.002 |
| $VO_2$peak | 0.45 (0.33–0.67) | <0.01 | 0.70 (0.55–0.86) | 0.001 |
| MIP | 0.75 (0.65–0.77) | <0.01 | 0.82 (0.77–0.94) | 0.002 |
| MEP | 0.83 (0.73–0.91) | <0.01 | 1.06 (0.87–1.5) | 0.525 |

HPS: hepatopulmonary syndrome; VHC: hepatitis virus C; MELD: Model for End-Stage Liver Disease; 6MWT: six-minute walk test; $VO_2$peak: peak oxygen consumption; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; HR: hazard ratio. Adjusted analysis for age, diagnosis, 6MWT, $VO_2$peak, MIP and MEP (*P*<0.2).

## DISCUSSION

The impairment in the functional conditions and exercise capacities of individuals with cirrhosis has been described in the literature for some time and with some frequency. First, with the use of a pilot study, we identified the association between functional condition and respiratory muscle strength with the classification of liver disease, according to the Child Pugh Score[19].

Further investigating this association, Dharancy et al.[20] found that in patients with LT, $VO_2$peak was normal in only 11.9% of the cases, and those patients demonstrating values less than 60% of the predicted value had higher mortality than those with values greater than or equal to 60% of the predicted value. Galant et al.[21] found that individuals with alcoholic cirrhosis with a $VO_2$peak of less than 14 mL/kg demonstrated a 60% mortality in three years, whereas those with a $VO_2$peak above that value had a mortality of 20% in the same period.

Following this reasoning and other previous study results, we identified that individuals with cirrhosis who walked less than 410 meters in the 6MWT and who had an MIP lower than -70 $cmH_2O$ and a $VO_2$peak lower than 17 mL/kg presented with poor survival and that the 6MWT was the most reliable variable to verify this outcome[22].

Thus, we believe that the waiting time for LT favored the appearance of several complications, including HPS, and that patients with cirrhosis and HPS arrive for the performance of this procedure with worse physical conditions, which may cause more postoperative complications as well as complications during the period in which they are hospitalized. The results of this study demonstrate that both patients with cirrhosis without HPS and those with HPS demonstrate values below predicted values with regard to functional condition, exercise capacity and respiratory muscle strength; however, the HPS group had a significantly worse performance in all the tests compared with the non-HPS group, corroborating our initial hypothesis.

In this study, patients with HPS presented a longer MV time after LT than patients without HPS. However, it is important to discuss the reasons that led to this result. Similar to patients with chronic obstructive pulmonary disease, patients with HPS tend to have lower prior arterial oxygenation, especially in our population. To improve diagnostic accuracy, we chose patients with a P(Aa) $O_2$ greater than 20 mmHg. Since the diagnosis of this syndrome is still a major challenge, many ICU professionals are not aware of this previous patient situation and, in a conservative manner, delay the weaning process, thus waiting for the normalization of arterial oxygenation, which is not corrected immediately after the procedure. On the other hand, the greater functional and muscular impairments in patients with HPS compared with those in patients without HPS may interfere with the tolerance for the exchange of controlled ventilatory modes with spontaneous ventilatory modes. Unfortunately, in this study, we could not identify which of these factors were predominant for the delay in the weaning process in the HPS group.

Regarding the need to use NIV, the conditions were similar. After extubation, patients with HPS may have lower arterial oxygenation values; conservatively, the professionals involved may opt for the use of this ventilatory support. However, in this aspect, we were able to identify that of the 12 cases of NIV use in the HPS group, 10 were due to the use of accessory musculature, and only two were due to hypoxemia. In the group without HPS, the two cases in which the NIV was used were with the use of accessory musculature. In only two cases, extubation failure occurred, and both of these cases were in the HPS group. These data may suggest that, perhaps, the delay in the weaning process occurred due to a worse functional and muscular condition as well as consequent intolerance to the evolution process of ventilatory modes rather than due to oxygenation alone. The consequence is a longer ICU stay and longer hospital stay.

There was no difference in mortality at 30 days after LT. This result can be explained by the fact that this outcome is more related to transoperative complications, such as hemorrhage and infections, and both groups were very similar with regard to the time of ischemia of the organ to be transplanted, the presence of hypertension pulmonary function and coagulation factors, and surgery time. In addition, it is important to point out that during this period, the patients have at their disposal the hospital structure, with services such as nutritionists, physiotherapists, nurses and doctors, 24 hours a day. This differentiated assistance may influence short-term mortality.

We did not find data in the literature that allowed us to compare or discuss these results in more depth. Thus, it is important to evaluate mortality during a longer period, where the worst functional condition and the worst exercise capacity can play more fundamental roles.

Previous studies have shown that there is a loss in muscle strength and exercise capacity of cirrhotic individuals awaiting liver transplantation, and that this could interfere with the waiting course for this procedure[23,24]. We verified that patients with cirrhosis diagnosed with HPS had a worse survival at two years after the procedure than patients without HPS and that the $VO_2$peak, distance walked on the 6MWT and MIP were independent predictors of mortality; this strengthens our idea that HPS can, through changes in oxygenation and gas exchange, affect exercise capacity and functionality and can be a negative aspect in the course of waiting for LT, thus contributing to the lower survival demonstrated by these patients after this procedure. This result corroborates the findings of Fallon et al.[25], who compared patients with cirrhosis and HPS with patients with cirrhosis without HPS and verified, through a specific questionnaire, a worse quality of life, especially in the general health aspect, and a lower post-LT survival in those who had the HPS diagnosis compared with those without HPS.

This result reinforces the idea that it may be necessary to develop a more specific rehabilitation program for this population, which will reduce the physical inactivity present in these patients and improve posttransplant results. Therefore, further studies should be performed so that we can better discuss these results.

Our study has some limitations, such as the absence of specific markers of muscle mass, muscle strength and nutritional status.

## CONCLUSION

The group of patients with cirrhosis diagnosed with HPS presented with a worse functional condition, exercise capacity and respiratory muscle strength when compared to the group of patients with cirrhosis without HPS. This same group remained longer in MV, needed more NIV, and stayed more days in the ICU and in the hospital after LT than the group of patients without HPS. There was no difference in mortality at 30 days after LT, but patients with HPS had a shorter survival two years after this procedure than patients without HPS. The 6MWT, $VO_2$peak and MIP were considered independent predictors of mortality.

### Authors' contribution

Pereira JLF, Galant LH: data collection and text writing. Rosa LHT: data collection. Garcia E, Brandão ABM: selection and diagnosis of patients. Marroni CA: selection, diagnosis of patients and technical guidance.

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**RESUMO** – **Contexto** – A síndrome hepatopulmonar (SHP) é uma complicação associada à cirrose que pode contribuir para piora da capacidade de exercício e menor sobrevida após o transplante hepático (TxH). **Objetivo** – Avaliar a capacidade de exercício, as complicações e a sobrevida após TxH em cirróticos com SHP e comparar com os resultados de cirróticos sem esse diagnóstico. **Métodos** – Estudo de coorte prospectivo, composto inicialmente por 178 pacientes, dos quais 90 foram submetidos ao TxH (42 com SHP e 48 sem SHP). Foi realizada uma avaliação prévia composta pelo teste de caminhada dos seis minutos (TC6M), teste ergométrico e manovacuometria. Os submetidos ao TxH tiveram avaliados o tempo de ventilação mecânica (VM), uso de ventilação não invasiva (VNI), e a sobrevida dois anos após o procedimento. Na análise estatística utilizamos os testes de Kolmogorov-Smirnov, o teste *t* de Student, o teste do quadrado de associação linear, a curva de sobrevida de Kaplan Meier. Os dados foram analisados no programa *SPSS* 16.00 sendo considerado significativo $P<0,05$. **Resultados** – O grupo SHP apresentou menor pico de consumo de oxigênio ($VO_2$pico) (14,2±2,3 vs 17,6±2,6) $P<0,001$, e menor distância percorrida no TC6M (340,8±50,9 vs 416,5±91,4) $P<0,001$ antes do TxH. Os pacientes com SHP transplantados permaneceram mais horas em VM (19,5±4,3 vs 12,5±3,3) $P=0,02$, necessitaram mais de VNI (12 vs 2) $P=0,01$, e tiveram menor sobrevida dois anos após o procedimento ($P=0,01$). **Conclusão** – Pacientes com SHP apresentaram pior capacidade de exercício antes do TxH, mais complicações e menor sobrevida após a realização desse procedimento.

**DESCRITORES** – Cirrose hepática. Síndrome hepatopulmonar. Transplante hepático.

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