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Research Article

Exercise Capacity and Survival after Liver Transplant in Cirrhotic Patients with Hepatopulmonary Syndrome

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Abstract

Introduction: Hepatopulmonary syndrome (HPS) is a complication associated with cirrhosis which may contribute to the worsening of exercise capacity and poor survival after liver transplant (LTx). The aim of this study was to compare survival 2 years after LTx between cirrhotic patients diagnosed with HPS and cirrhotic patients without HPS, and identify independent predictors for this outcome.

Materials and Methods: A prospective cohort of four years, consisting of 178 patients (92 with and 86 without SHP) diagnosed with cirrhosis and potential candidates to LTx. All patients underwent a preliminary assessment made by the six-minute walk test (6MWT), ergometric test and manovacuometry. For the statistical analysis we used the Kolmogorov-Smirnov test, Student's t test, the linear association square test, the Kaplan Meier survival curves and Cox regression.

Results: Patients with cirrhosis without HPS diagnosis had higher survival in a period of 2 years after transplantation($p = 0.01$). There was a 17% higher survival rate with increasing distance in the 6MWT (HR = 0.83, CI95% = 0.73-0.94, $p = 0.003$), as well as improved oxygen consumption peak (VO_2peak) increased by 30% survival (HR = 0.70, CI95% = 0.57 - 0.82, $p = 0.001$) and a higher maximum inspiratory pressure (MIP) increased by 15% survival (HR = 0.85, IC95% = 0.75-0.92, $p = 0.002$).

Conclusion: Patients with cirrhosis without HPS diagnosis have a higher survival within 2 years after LTx. The HPS, 6MWT, VO_2peak and MIP were considered independent predictors for this outcome.

Keywords: *Six Minute Walk Test; Peak Oxygen Consumption; Respiratory Muscle Strength*

Abbreviations

ADL: Activities of Daily Living; AT: Anaerobic threshold; BMI: Body mass index; cmH_2O: Centimeters of water; CEC: Contrast echocardiography; FEV1:Forced expiratory volume in the first second; FVC: Forced vital capacity; HCV: Hepatitis C virus; HPS: Hepatopulmonary Syndrome; HR: Hazard Ratio; LTx: Liver Transplantation; MELD: Model for end stage liver disease; MEP: Maximum Expiratory Pressure; MIP: Maximum Inspiratory Pressure; µm: Micrometer; mmHg: Millimeters of mercury; PaO_2: Pressure of oxygen in arterial blood; $P(A\text{-}a)O_2$: Alveolar-arterial oxygen gradient; VO_2máx: Maximum consumption of oxygen; VO_2peak: Oxygen Consumption Peak; 6MWT: Six Minute Walk Test

Introduction

Hepatic cirrhosis is characterized by the diffuse replacement of the normal liver structure by nodules with abnormal structure surrounded by fibrosis. It occurs in the final stage of a series of liver pathological processes due to various causes [1]. Its complications include the metabolic changes associated with malnutrition in the patients, who lose large amounts of muscle mass and then exhibit changes in functionality and a condition of physical inactivity. The combination of all these factors negatively influences the Activities of Daily Living (ADL) and quality of life of this population [2-5].

The treatment of cirrhotic patients is complex and necessarily broad, with poor long-term survival prospects. Liver transplantation (LTx) arguably allows a higher survival rate for these patients and also reduces the treatment cost [6-8]. Thus, many candidates spend a long time on the waiting list, which enhances the risk of development of new complications that in turn worsen their functionality.

Although its association with the severity of liver disease is controversial, hepatopulmonary syndrome (HPS), which is characterized by a clinical trial involving liver disease and/or portal hypertension, intrapulmonary vascular dilatation and abnormal arterial oxygenation (Pressure of oxygen in arterial blood (PaO_2) less than 70 millimeters of mercury (mmHg) or alveolar-arterial oxygen gradient ($P(A-a)O_2$), greater than 20 mmHg in room air), is one of the complications associated with cirrhosis. It has a prevalence of 16% to 24% and presents with very unspecific signs and symptoms [9-15].

Recently we found in our population of cirrhotic patients diagnosed with HPS a loss in relation to exercise capacity suggesting that changes in oxygenation and gas exchange can contribute to a worsening of the functionality and consequently the quality of life of these patients [16]. However, the scarcity of studies addressing physical aspects of HPS has hindered the identification of their impact on the natural history of liver disease, including post LTx period.

Thus, the aim of this study was to compare the survival of cirrhotic patients diagnosed with HPS and cirrhotic patients without this diagnosis in a period of two years after the LTx, and identify independent predictors for this outcome.

Materials and Methods

This prospective cohort study over four years was composed of a convenience sample of 178 patients from a single centre (92 with HPS and 86 without HPS) with a diagnosis of cirrhosis due to hepatitis C virus (HCV) or alcohol use. All of the patients were part of a group of approximately 600 individuals who were monitored by the Liver Transplant Clinic of the Santa Casa de Misericordia Hospital Complex (Ambulatório de Transplante Hepático do ComplexoHospitalar Santa Casa de Misericórdia), Porto Alegre, Rio Grande do Sul, Brazil. All of the patients were also potential candidates for LTx. After inclusion in the study, all of the patients signed a free and informed consent form and underwent a preliminary assessment made by the Six Minute Walk Test (6MWT), ergometric test and manovacuometry. After they were followed for four years.

The exclusion criteria included prior significant obstructive ventilatory impairment, defined by a Tiffeneau index less than 0.70 with a forced expiratory volume in the first second (FEV1) less than 80% of predicted; prior significant restrictive ventilatory impairment, defined by a forced vital capacity (FVC) less than 70% of predicted; or other comorbidities not related to liver disease, significant orthopedic disorders, or absolute contraindications to perform submaximal tests and the presence of an intracardiac shunt.

The project was approved by the Research Ethics Committee of the hospital complex under opinion No. 331.068.

Hepatopulmonary syndrome - diagnosis

HPS diagnoses were determined according to predetermined criteria. Cirrhotic patients were subjected to contrast echocardiography

(CEC), in which agitated saline solution was administered via the antecubital vein. The resulting micro bubbles from this procedure had a diameter of 60 to 90 micrometers (μm), larger than the normal capillary bed, which has a diameter of 8 to 15 μm. Thus, these bubbles normally render opaque only the right heart chambers. However, with the loss of the anatomical barrier due to dilatation of the intrapulmonary capillary bed, the microbubbles can reach the left chambers between three and six cycles after their appearance in the right chambers. In combination with CEC, blood gas values were evaluated, especially the $P(A\text{-}a)O_2$, as the isolated analysis of the PaO_2 can underestimate the true degree of hypoxemia. It was decided that a $P(A\text{-}a)O_2$ greater than 20 mmHg was necessary because of its improved accuracy, as reported in previous studies [14,15].

Ergometric test

Oxygen consumption peak (VO_2peak) was used to evaluate exercise capacity. In this evaluation, each patient was monitored with a three-channel electrocardiograph (Dixtal) coupled to an oscilloscope. Initially, a 15-minute rhythm recording based on the derivation corresponding to D2 was obtained from the patient at rest. Subsequently, a heart rhythm recording (D2 derivation) and an electrocardiogram trace (derivation corresponding to V1, aVF, CM5) were simultaneously obtained from the patient during a 15-minute exercise period. The modified Bruce protocol with gas exchange analysis was used. The exercise was interrupted if the patients had symptoms that would prevent its continuation and/or represent a risk, such as the appearance of complex ventricular arrhythmias, intraventricular and/or atrioventricular conduction disorders or even bradyarrhythmias. In the analysis, only tests in which the patients reached the anaerobic threshold (AT) were considered to ensure that everyone had reached a submaximal exercise level. The AT was expressed in relation to VO_2peak in ml/min (STPD, standard temperature and pressure, dry) and was identified by the VO_2peak value at which the respiratory exchange ratio ($R = VCO_2/VO_2$) was equal to or greater than one and continued increasing in subsequent respiration cycles. The analysis of the occurrence of arrhythmias was especially valued, including the total number of ventricular extrasystoles, the number of pairs of ventricular extrasystoles and the number of episodes of sustained and non-sustained ventricular tachycardia both at rest and during exercise [17].

Six-minute walk test (6MWT)

The 6MWT was used to assess the patients' functional condition. This test was performed in a 30-meter flat, straight hallway that was free of any type of obstacles. Before starting the test, all patients were provided instructions by the evaluator; during the test, they received standardized verbal encouragement every minute to walk the longest distance possible. The distance walked was measured at the end of the test. The patients were monitored by respiratory rate, heart rate and peripheral oxygen saturation using a Nonin oximeter (9500, USA). The sensation of dyspnea and fatigue in the lower limbs was assessed using the modified Borg scale (0 - 10 scale) according to the American Thoracic Society. Except for the distance walked, all variables were collected both before the test and after the end of the test [18].

Manovacuometry

To measure respiratory muscle strength, a digital manovacuometer (MVD 500, Globalmed®) was used, which was calibrated before each data collection session. To assess maximal inspiratory pressure (MIP), the patient was asked to perform a maximal expiration to the level of residual volume and, after the equipment was correctly positioned in the mouth, to achieve a maximum forced inspiration. To evaluate maximum expiratory pressure (MEP), the patient was asked to initiate the maneuver starting at total lung capacity, which was followed by a maximal forced expiration. To perform the maneuvers, the equipment was positioned correctly in the patient's mouth. A nose clip was used to prevent air leaks, and the manovacuometer had a purge hole leak.

The maneuver was required to be maintained for at least one second and to have a total time of at least two seconds to verify the peak pressure. The results were obtained after five maneuvers with an interval of at least one minute between them, when a minimum of three acceptable maneuvers had been performed, i.e., no more than 10% difference between their values. Then, the highest pressure in

centimeters of water (cmH_2O) was recorded, and the normal values recommended by the Brazilian Society of Pneumology and Tisiology (Sociedade Brasileira de Pneumologia e Tisiologia) were used [19,20].

Data Analysis

To verify sample homogeneity was used Kolmogorov-Smirnov test, to compare continuous variables the Student t test and to compare categorical variables the square test and linear association. For the analysis of survival in both groups we used the Kaplan Meier survival curve, and to analysis of independent predictors was used Cox regression.

Results

Of the 178 patients evaluated, 90 (42 with HPS and 48 without SHP) underwent liver transplantation and were followed for a period of 2 years after the procedure. Among others, 4 died while waiting on the waiting list and 84 remained under monitoring by the Liver Transplant Clinic of the Santa Casa de Misericordia Hospital Complex.

In Table 1 we present the characteristics of the sample. There was no significant difference between cirrhotic group diagnosed with HPS and the cirrhotic group without this diagnosis with regard to age, gender, body mass index (BMI), cirrhosis etiology, Child Pugh score and Model for end stage liver disease (MELD).

Variable	All (90)	SHP+ (42)	SHP- (48)
Age (years)	60.1 ± 7	61.2 ± 6.9	59.2 ± 7
BMI	25.7 ± 5	24.8 ± 1.5	26.5 ± 6.6
Gender			
Male (n)	55 (61.1)	23 (54.8)	32 (66.7)
Female (n)	35 (38.9)	19 (45.2)	16 (33.3)
Etiologyofcirrhosis			
Alcohol (n)	31 (34.4)	17 (40.5)	14 (29.2)
HCV (n)	59 (65.6)	25 (59.5)	34 (70.8)
Child-Pugh Score			
A (n)	37 (41.1)	15 (35.7)	22 (45.8)
B (n)	35 (38.9)	16 (38.1)	19 (39.6)
C (n)	18 (20)	11 (26.2)	7 (14.6)
MELD	18.5 ± 2.4	18.4 ± 0.6	18.6 ± 3.2
Late shunt			
Yes (n)	42 (46.7)	42 (100)	0**
No (n)	48 (53.3)	0	48 (100)
6MWT (meters)	364.9 ± 52.4	334 ± 19.2	392 ± 57.2**
VO_2peak(ml/kg)	16.4 ± 2.2	14.9 ± 1.6	16.8 ± 2.6**
MIP (cmH_2O)	52 (-60 a 103)	-47.8 ± 4.8	66.6 ± 11.8**
MEP (cmH_2O)	61 (46 a 103)	58.5 ± 5.5	70.8 ± 14.3**

PaO_2 (mmHg)	80.6 ± 12.1	68.2 ± 3.6	91.5 ± 3**
$P(A\text{-}a)O_2$ (mmHg)	17.3 ± 6.7	24.2 ± 1.6	11.3 ± 1.6**
Numberofevents (Deaths)	17 (18.9)	11 (26.1)	6 (12.5)*

Table 1: *Baseline characteristics of the sample (n = 90).*

*SHP+ = With Hepatopulmonary Syndrome; SHP- = Without Hepatopulmonary Syndrome; BMI: Body Mass Index; HCV: Hepatitis C Virus; MELD: Model for end stage liver disease; 6MWT: Six minute walk test; VO2peak: Peak oxygen consumption; MIP: Maximum inspiratory pressure; MEP: Maximum expiratory pressure; PaO_2: Pressure of oxygen in arterial blood; P(A-a)O: Alveolar-arterial oxygen gradient. Results presented as ratios; average and standard deviation; except MIP and MEP; presented as median (min-máx). Square test and linear association (categorical variables) and Student t test (continuous variables); *p < 0.05; **p < 0.001*

However, the cirrhotic group with HPS has a lower PaO2 (68.2 ± 3.6 vs 91.5 ± 3) p < 0.001, a larger P(A-a)O2 (24.2 ± 1.6 vs 11 3 ± 1.6) p < 0.001, a worse performance in the 6MWT (334 ± 19.2 vs 392 ± 57.2) p < 0.001, lower VO2 peak (14.9 ± 1.6 vs 16.8 ± 2, 6) p < 0.05 lower MIP (- 47.8 ± 4.8 vs - 66.6 ± 11.8) p < 0.001 lower MEP (58.5 ± 5.5 vs. 70.8 ± 14 3) p < 0.001 and highest number of deaths (11 vs 6) p < 0.05.

Figure 1 shows the Kaplan Meier survival curve. The cirrhotic group without the diagnosis of HPS had longer survival in a period of 24 months when compared to cirrhotic group diagnosed with HPS (p = 0.01).

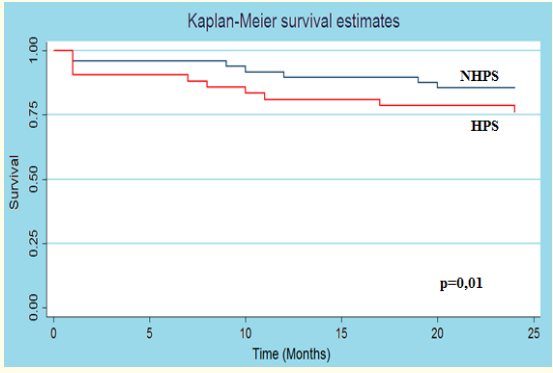

Figure 1: *Kaplan-Meier survival estimates in 24 months.*

NSHP- Without Hepatopulmonary Syndrome

HPS – With Hepatopulmonary Syndrome

In univariate Cox analysis (Table 2), we can see that the variables etiology of cirrhosis, Child-Pugh score, MELD, 6MWT, VO2 peak, MIP and MEP proved as predictors that significantly influence mortality in this sample. Regarding the etiology, mortality among patients with cirrhosis due to HCV was 75% lower (HR = 0:25, CI95% = 0.09 - 0.68, p = 0.007) when compared to the group of subjects with cirrhosis due to alcohol (HR = 1). The presence de HPS represented a mortality rate about 3 times higher (HR = 3.45 CI 95% = 2.15 - 5.41, p < 0.001). Regarding the Child-Pugh score, there was no difference in survival between the classifications A and B (HR = 1.65, CI95% = 0.27-9.86, p = 0.584), but the C class presented a mortality rate about 18 times higher when compared with individuals classified as Child-Pugh A (HR = 17,9, CI95% = 3.98 - 80.8, p < 0.001). The increase in the MELD score decreases by up to 33% survival in the sample (HR = 1.33, IC95% = 1.11 - 1.60%, p = 0.002). On the other hand, increasing the distance traveled in 6MWT increase in survival by 15% in the sample (HR =

0.85, CI95% = 0.79 - 0.90, p < 0.001) and VO_2peak increases up to 52% in the same (HR = 0.49, CI95% = 0.35 - 0.69, p < 0.001). Likewise, the MEP proved to be influential in patient survival. Increasing this variable implies the reduction of the chances of mortality by 17% (HR = 0.84, CI95% = 0.77 - 0.92, p < 0.001). What about the MIP, an increase of this variable represents a reduction of up to 27% mortality (HR = 0.73 CI95% = 0.62 - 0.78, p < 0.001).

	Notadjusted analysis		**Adjusted analysis**	
Variable	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
Gender				
Female	1.0			
Male	0.6 (0.26 - 1.76)	0.426		
HepatopulmoarySyndrome		< 0.001		0.001
No	1.0		1.0	
Yes	3.45 (2.15 - 5.41)		3.25 (2.09 - 5.15)	
Diagnosis				
Cirrhosis due to alcohol	1.0		1.0	
Cirrose due to HCV	0.25 (0.09 - 0.68)	0.007	2.19 (0.22 - 21.7)	0.502
Child-Pugh				
Classe A	1.0			
Classe B	1.65 (0.27 - 9.86)	0.584	1.58 (0.18 - 13.8)	0.677
Classe C	17.9 (3.98 - 80.8)	< 0.001	3.45 (0.33-35.7)	0.297
Meld	1.33 (1.11 - 1.60)	0.002	1.24 (0.86-1.8)	0.242
6MWT	0.85 (0.79 - 0.90)	< 0.001	0.83 (0.73-0.94)	0.003
VO_2peak	0.49 (0.35 - 0.69)	< 0.001	0.70 (0.57-0.82)	0,001
MIP	0.73 (0.62 - 0.78)	< 0.001	0.85(0.75-0.92)	0.002
MEP	0.84 (0.77 - 0.92)	< 0.001	1.06 (0.87-1.3)	0.533

Table 2: *Univariate and multivariate analysis of the variables under study.*

HCV: Hepatitis C Virus; MELD: Model for end stage liver disease; 6MWT: Six minute walk test; VO_2peak: Peak oxygen consumption; MIP: Maximum inspiratory pressure; MEP: Maximum expiratory pressure; PaO_2: Pressure of oxygen in arterial blood; $P(A\text{-}a)O_2$: Alveolar-arterial oxygen gradient. HR= Hazard Ratio; ‡ Analysis adjusted by age; diagnosis; Child-Pugh Score; MELD; 6MWT; VO_2peak; MIP and MEP (p < 0.2).

In the multivariate analysis (Table 2) adjusted for age, etiology, Child-Pugh score, MELD, 6MWT, VO_2 peak, MEP and MIP were selected those variables with p < 0.2 in the univariate Cox model. In it, the HPS, 6MWT, VO_2 peak and MIP remain as independent predictors of mortality in the studied sample. The presence de HPS remain represented a mortality rate about 3 times higher (HR = 3.25 CI95% = 2.09 - 5.15, p = 0,001) There was a 17% higher survival rate with increasing distance in the 6MWT (HR = 0.83, CI95% = 0.73-0.94, p = 0.003), as well as a better VO2peak increased by up to 30% survival (HR = 0.70 CI95% = 0.57-0.82, p = 0.001) and greater MIP increased by up to 15% patient survival (HR = 0.85 95% CI 0.75-0.92, p = 0.002).

Discussion

Previously identified in the literature that there is an impairment in cirrhotic exercise capacity when compared to the general population. Dharancy., *et al*. found that in candidates for liver transplantation the maximum consumption of oxygen (VO_2max) was normal in only 11.9% of cases, and that those patients with values less than 60% predicted, had a higher mortality than those with values greater than or equal to 60% of predicted [21]. Likewise, Galant., *et al*. found that patients with alcoholic cirrhosis who had a VO_2 peak less than 14 ml/kg showed a mortality of 60% in three years, while those with a VO_2 peak above this value had mortality rate of 20% in the same period [22].

When the 6MWT was the instrument used, the results also show impairment in cirrhotic patients. Carey., *et al*. found that candidates for liver transplantation who walked less than 250 meters in the test had a higher mortality than those who walked more than 350 meters [23]. Moreover, in our previous studies we have found that the advancement of liver disease, with clinical deterioration of patients, as evidenced by the Child Pugh Score, interferes in the distance covered on the 6MWT, and this result was similar when the variable under study was respiratory muscle strength [24].

Although the HPS is present in a reasonable percentage of cirrhotic patients, few studies have addressed its impact on this population exercise capacity, which somewhat limits its real understanding in the course of the disease. Therefore, we deem relevant at first evaluate the exercise capacity of potential cirrhotic candidates for liver transplantation with the diagnosis of HPS and compare with cirrhosis without this diagnosis. The results showed that, in our population, the cirrhotic group with HPS diagnosis had a worse VO_2peak, a smaller distance in the 6MWT and lower respiratory muscle strength [16].

In this new study, we found that in addition to having lower exercise capacity, cirrhotic patients with HPS diagnosis had worse survival at 24 months after the procedure. We identified although the VO_2 peak, the distance covered in 6MWT and MIP were independent predictors of mortality.

As only 2 patients in each group died in the first 30 days following the procedure, period in which this outcome is more associated with intraoperative factors and immediate postoperative, such as bleeding and sepsis, we believe that the HPS may through the oxygenation and gas exchange alterations, affect exercise capacity, functionality, and be a negative aspect in the course of waiting for the LTx, contributing to poor survival these patients, as evidenced also by Fallon., *et al*. which compared cirrhotic patients with HPS and cirrhotic patients without HPS and verified through a specific questionnaire, poorer quality of life, especially in the aspect of overall health, and a lower survival rate after liver transplantation in those who had a diagnosis of HPS [25]. This reinforces the idea that perhaps the development of a more specific rehabilitation program is needed for this population, which enables to reduce physical inactivity, very present in these patients, and improve post-transplant results. Thus, further studies should be conducted so we can better discuss these results.

Conclusion

In conclusion, the group of cirrhotic patients with HPS diagnosis had lower survival 24 months after liver transplantation, compared to cirrhotic patients without this diagnosis. The presence de HPS, the distance covered in the 6MWT, VO_2peak and MIP were considered independent predictors of mortality in this population.

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