

# Unmasking Hypoxia in Cirrhosis Patients: Six-Minute Walk Test as a Screening Tool for Hepatopulmonary Syndrome

## Abstract

**Background:** Hepatopulmonary syndrome (HPS) is one of the complications of advanced cirrhosis which has a serious impact on prognosis of patient. Finding arterial deoxygenation early and initiating higher-level treatment is one of the most critical strategies in the therapy of HPS. In this study, we aimed to assess the utility of six-minute walk test (6MWT) in the diagnosis of HPS. **Materials and Methods:** We have enrolled 100 consecutive cirrhosis patients referred to the Liver Clinic of a tertiary care centre of India for >1 year. The Child-Pugh score and the MELD score were used to determine the severity of cirrhosis. All the patients underwent transthoracic contrast echocardiography, arterial blood gas measurements on room air, 6MWT, and chest imaging. **Results:** A total of 100 patients were included in the study after fulfilling the inclusion criteria. HPS was present in 21 out of 100 patients (21%). Median (twenty fifth to seventy fifth percentile) MELD score in patients with HPS was 29 (26–33), which was significantly higher as compared to patients without HPS 22 (14.5–26);  $P < .0001$ . The 6MWT was positive in 20 (95.23%) HPS patients, while only 1 patient (4.77%) of HPS had negative 6MWT. If 6MWT is positive, then there was 76.92% probability of HPS and if 6MWT is negative, then 98.65% chances of no HPS. **Conclusion:** The 6MWT is a simple and effective screening test for HPS, it helps in identifying the patients early who have a potential to deteriorate. This simple intervention would help in prioritizing patients for liver transplantation as liver transplant is the only effective treatment for HPS.

**Keywords:** Hepatopulmonary syndrome, hypoxia, liver transplant, MELD score

## Introduction

Cirrhosis is an end-stage liver disease marked by hepatic architectural distortion and the production of regenerating nodules as a result of increased hepatic fibrosis. Various complications can develop due to cirrhosis and affect the life expectancy of the patients. Major complications of cirrhosis are variceal hemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome (HPS), and hepatocellular carcinoma. HPS is one of the complications of advanced cirrhosis which have a serious impact on the prognosis of the patient. HPS is a classical triad of chronic liver disease, arterial deoxygenation due to pulmonary gas exchange abnormalities, and diffuse intrapulmonary vascular dilatation (IPVD).<sup>[1]</sup> Severe hypoxemia ( $PO_2 < 60$  mmHg) in cirrhosis patients without any cardiovascular disease strongly suggests HPS.<sup>[2-4]</sup> Diagnostic

criteria for HPS are (a) partial pressure of oxygen ( $PaO_2$ )  $< 80$  mm Hg, or alveolar-arterial oxygen gradient ( $A-aO_2$ )  $\geq 15$  mm on room air ( $A-aO_2 > 20$  mm Hg in patients  $> 64$  years), (b) pulmonary vascular dilatation as shown by radioactive lung-perfusion scanning or positive contrast-enhanced echocardiography, and (c) portal hypertension.

This syndrome is often under-diagnosed, due to the fact that most of the affected patients are either asymptomatic or present vague complaints of dyspnea and fatigue. Prevalence of HPS in cirrhosis varies from 4% to 47%, depending upon the diagnostic criteria used and the population studied.<sup>[5-8]</sup> Sufficient data about HPS in Indian patients are not available despite the high prevalence of liver cirrhosis in India and advances in our knowledge of HPS. Currently, the only definitive treatment of HPS is liver transplantation.

Finding arterial deoxygenation early and initiating higher-level treatment is one of the most critical strategies in the therapy of

**Abhishek Singhai,  
Manaswinee Mallik,  
Pragya Jain<sup>1</sup>**

Department of Medicine, All India Institute of Medical Sciences, <sup>1</sup>Department of Ophthalmology, Peoples College of Medical Sciences, Bhopal, Madhya Pradesh, India

## Address for correspondence:

Dr. Abhishek Singhai,  
Department of Medicine,  
All India Institute of  
Medical Sciences, Bhopal,  
Madhya Pradesh, India.  
E-mail: drabhisheksinghai@gmail.com

**Received:** 03 June 2021

**Revised:** 16 February 2022

**Accepted:** 04 April 2022

**Published:** 29 June 2022

## Access this article online

**Website:** www.advbiores.net

**DOI:** 10.4103/abr.abr\_150\_21

## Quick Response Code:



**How to cite this article:** Singhai A, Mallik M, Jain P. Unmasking hypoxia in Cirrhosis patients: Six-minute walk test as a screening tool for hepatopulmonary syndrome. Adv Biomed Res 2022;11:50.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

HPS. A simple six-minute walk test (6MWT) to look for inducible hypoxia for a patient who looks comfortable and is not hypoxic at rest, may help in the early detection of HPS and in initiating early higher-level care. The 6MWT aids in assessing the functional capacity of patients with cardiopulmonary disease. In this study, we aimed to assess the utility of 6MWT in the diagnosis of HPS.

## Materials and Methods

### Study design and study subjects

This was a cross-sectional hospital-based study. We have enrolled 100 consecutive cirrhosis patients referred to the Liver Clinic of a tertiary care center in India for >1 year. Patients with underlying cardiovascular disease with New York Heart Association (NYHA) Functional Classification grade 2 and more and respiratory diseases were excluded from this study. Institutional ethical board approval (No.IHEC-LOP/2019/MD0089) and written informed consent from participants were taken before starting the study.

### Data collection and variables

All patients participating in this study have been confirmed for liver cirrhosis by clinical, laboratory, ultrasonography, and liver elastography as well as on liver histology, when a liver biopsy specimen was available. The Child-Pugh score and the MELD score were used to determine the severity of cirrhosis. If a patient had tense ascites, therapeutic ascitic tapping was performed before subjecting to further tests. Clinical and laboratory assessment was performed as per standard protocol in cirrhosis patients including the grade of ascites, grade of encephalopathy, liver function test, serum creatinine, prothrombin time, serum albumin, hepatitis B, hepatitis C, and any other investigations to detect etiology of cirrhosis. Contrast-enhanced transthoracic echocardiogram was performed on all the subjects. At the start of the procedure, an intravenous cannula was secured in the right hand cubital vein of the patient, and 10 ml of agitated saline was injected into it. After five beats, echocardiography was used to assess the cardiac chambers. An intrapulmonary shunt was defined as the presence of microbubbles in the left atrium after five beats. A percutaneous radial artery puncture was used to obtain an arterial blood gas sample.

The difference between alveolar oxygen pressure (PAO<sub>2</sub>) and PaO<sub>2</sub> was used to determine A-a O<sub>2</sub>, with PAO<sub>2</sub> = [0.21 (barometric pressure-47)] (1.25PaCO<sub>2</sub>). A second sample was collected after 1 h in the upright position in all patients, and orthodeoxia was defined as a reduction in SaO<sub>2</sub> of >4% after changing from the supine to the upright position. The 6MWT was performed in an outdoor or indoor hospital setting; one healthcare worker supervised the test. A baseline oxygen saturation using a finger pulse oximeter probe was noted. Patients were asked to walk with their self-pace and oxygen saturation was measured

again at the end of 6 minutes. Positive 6MWT is defined as fall in SpO<sub>2</sub> level less than 94% or drop in SpO<sub>2</sub> by 3% or more from baseline.

### Statistical analysis

The categorical variables were expressed as numbers (*n*) and percentages, whereas the continuous variables were expressed as mean and median (percent). The Chi-square test or Fisher's exact test was used to compare categorical and continuous variables, while the student's *t*-test or Mann-Whitney U test was used to compare continuous and categorical variables. Significant difference is defined as *P* < 0.05.

## Results

A total of 100 patients were included in the study after fulfilling the inclusion criteria. Among them, 69% of the patients were males and 31% of the patients were females. In majority (63%) of the patients, body mass index (BMI, kg/m<sup>2</sup>) was 25–29.99 (overweight). Comorbidities were present in only 18 (18%) patients. Mean age (years) of the study subjects was 46.31 ± 9.5 with median (twenty fifth to seventy fifth percentile) of 45.5 (39–53) [Table 1]. Diabetes mellitus was the most common comorbidity (15%), followed by coronary artery disease (4%), hypothyroidism (3%), systemic hypertension (2%), and chronic kidney disease (1%).

In our study, the most common cause of cirrhosis was alcohol (44%) followed by nonalcoholic steatohepatitis (NASH) (15%), hepatitis B (14%), idiopathic (13%), and hepatitis C (6%). Less common causes of cirrhosis were autoimmune hepatitis, biliary, congestive cardiac failure,

**Table 1: Distribution of sociodemographic characteristics of study subjects**

Sociodemographic characteristics	Frequency	Percentage
Age (years)		
Mean±SD		46.31±9.5
Median (twenty fifth to seventy fifth percentile)		45.5 (39-53)
Range		21-70
Gender		
Female	31	31.00%
Male	69	69.00%
BMI (kg/m <sup>2</sup> )		
18.5-24.99 (normal)	24	24.00%
25-29.99 (overweight)	63	63.00%
≥30 (obese)	13	13.00%
Mean±SD		26.23±3.11
Median (twenty fifth to seventy fifth percentile)		26 (25-28)
Range		19-33
Comorbidities		
No	82	82.00%
Yes	18	18.00%

and Wilson's disease. Cyanosis was not seen in any patient and clubbing was present in only 1 patient. Mean duration since diagnosis (years) of cirrhosis was  $4.87 \pm 3.3$  with a median (twenty fifth to seventy fifth percentile) of 4 (2.75–7). Mean value of MELD score of study subjects was  $22.39 \pm 7.06$  with median (twenty fifth to seventy fifth percentile) of 23 (17–27.25). In our study, majority of the patients were in Child Pugh class C (73%) followed by B (21%). Only six (6%) patients were in Child Pugh class A.

Mean value of SpO<sub>2</sub> at room air (%) and SpO<sub>2</sub> after 6MW (%) of study subjects was  $95.61 \pm 2$  and  $92.62 \pm 4.1$  with median (twenty fifth to seventy fifth percentile) of 96 (95–97) and 94 (91.75–95), respectively. HPS was present in 21 out of 100 patients (21%). Median (twenty fifth to seventy fifth percentile) MELD score in patients with HPS was 29 (26–33) which was significantly higher as compared to patients without HPS (22 (14.5–26);  $P < 0.0001$ ) [Table 2].

Prevalence of HPS was higher in Child Pugh class C patients (65.82%) compared to class B (26.58%) and class A (0%). ( $P = 0.004$ ) [Table 3].

The 6MWT was positive in 20 (95.23%) HPS patients, while only 1 patient (4.77%) of HPS had negative 6MWT [Table 4]. If 6MWT is positive, then there was 76.92% probability of HPS and if 6MWT negative, then 98.65% chances of no HPS. Among patients who did not have HPS, 92.4% of patients had negative 6MWT [Table 5]. The area under the receiver operating characteristic for 6MWT predicting HPS was 0.938 (0.872–0.977), thus demonstrating excellent diagnostic performance. It was statistically significant ( $P < 0.001$ ) [Figure 1].

## Discussion

The first recorded description of hypoxemia with liver diseases was by Flückiger in 1884. In 1977, Kennedy and

Knudson described classical findings in a case of chronic liver disease and invented the term “hepatopulmonary syndrome.”<sup>[9]</sup> At present, HPS is a widely known disease but it remains a rare entity as only cirrhosis patients have it. Majority of HPS patients (82%) are asymptomatic for lung involvement and are present with symptoms related to liver disease only. Among symptomatic patients' the most common complaint is an insidious onset of progressive dyspnea that usually develops after years of liver disease.<sup>[10]</sup> However, dyspnea in cirrhosis patients can be multifactorial and this symptom is often overlooked. Therefore diagnosis of HPS is delayed in most of the patients and dyspnea progresses. This progression may occur despite stable liver function.<sup>[11]</sup> A single center prospective study of 789 patients referred for liver transplantation reported that compared with patients without HPS, patients with HPS had a significant increase in hospital cost, prolonged intensive care unit stay, and prolonged hospital stay.<sup>[12]</sup> Only effective

**Table 2: Association of MELD score with HPS**

MELD score	No HPS (n=79)	HPS (n=21)	Total	P
Mean±SD	20.47±6.37	29.62±4.36	22.39±7.06	<.0001*
Median (twenty fifth to seventy fifth percentile)	22 (14.5-26)	29 (26-33)	23 (17-27.25)	
Range	8-33	22-36	8-36	

\*Mann Whitney test

**Table 3: Association of Child Pugh class with HPS**

Child Pugh class	No HPS (n=79)	HPS (n=21)	Total	P
A	6 (7.59%)	0 (0%)	6 (6%)	0.004*
B	21 (26.58%)	0 (0%)	21 (21%)	
C	52 (65.82%)	21 (100%)	73 (73%)	
Total	79 (100%)	21 (100%)	100 (100%)	

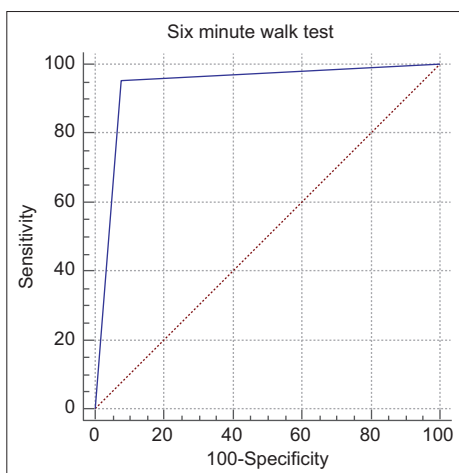
\*Fisher's exact test

**Table 4: Association of 6MWT with HPS**

6MWT	No HPS (n=79)	HPS (n=21)	Total	P
Negative	73 (92.4%)	1 (4.77%)	74	<.0001
Positive	6 (7.6%)	20 (95.23%)	26	
Total	79	21	100	

**Table 5: Sensitivity, specificity of 6MWT for predicting HPS**

HPS	6MWT
Sensitivity (95% CI)	95.24% (76.18-99.88%)
Specificity (95% CI)	92.41% (84.20-97.16%)
AUC (95% CI)	0.938 (0.872-0.977)
Disease prevalence (95% CI)	21% (13.49-30.29%)
Positive predictive value (95% CI)	76.92% (60.56-87.86%)
Negative predictive value (95% CI)	98.65% (91.50-99.80%)
Diagnostic accuracy	93%



**Figure 1: Receiver operating characteristic curve of 6MWT for predicting HPS**

treatment available for HPS is liver transplantation. Significant improvement in lung functions occurs within 1 year of transplantation.<sup>[13]</sup>

In our study, patients with HPS had more severe liver disease as measured by the MELD and Child Pugh scores. Haj *et al.*<sup>[14]</sup> also found association between HPS and the severity of liver illness. The authors looked on HPS in compensated cirrhosis patients who were ambulatory. They discovered positive association between HPS and severe cirrhosis, as measured by the Child Pugh score or the MELD. Similar findings were also found in other studies.<sup>[6,15,16]</sup>

Exercise capacity, functional condition, and respiratory muscle strength are all lower in cirrhotic individuals with HPS than in cirrhotic patients without HPS. Only 38% of candidates for liver transplantation had normal peak oxygen consumption, according to Parikh *et al.*,<sup>[17]</sup> and patients with values <60% of the expected value have a higher mortality rate than patients with values ≥60% of the predicted value. Marroni *et al.*<sup>[18]</sup> discovered that people with alcoholic cirrhosis who had reduced peak oxygen intake had a 60% mortality rate in the next three years. The 6MWT can be used to assess the functional status of the lungs. Correlation between the 6MWT and peak oxygen consumption is also well described in the literature.<sup>[19-21]</sup>

The 6MWT is a useful tool to screen patients for HPS with a sensitivity and specificity of 95.24% and 92.41%, respectively. Though our study's sample size is small, it serves as a springboard for larger studies to establish a cause-and-effect relationship between 6MWT and HPS. Other tests for diagnosis of HPS are transesophageal echocardiography (TEE), contrast pulmonary angiography, and macroaggregated albumin scanning. TEE allows direct visualization of microbubbles in the pulmonary veins as they enter the left atrium but it is more invasive and often avoided in this population due to the risk of bleeding from esophageal varices. Technetium 99m-labeled macroaggregated albumin scanning is an alternative method of confirming and quantifying shunt from IPVDs. Pulmonary angiography is invasive and, therefore, seldom performed in patients with suspected HPS. Large pulmonary arteriovenous malformations can be embolized through this procedure.

## Conclusion

The 6MWT is a simple and effective screening test for HPS, it helps in identifying patients early who have a potential to deteriorate. This simple intervention would help in prioritizing patients for liver transplantation as liver transplant is the only effective treatment for HPS. It can also be used as a prognostic indicator in patients with liver cirrhosis.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

- Weinfurter K, Forde K. Hepatopulmonary syndrome and portopulmonary hypertension: Current status and implications for liver transplantation. *Curr Hepatol Rep* 2020;19:174-85.
- Soulaidopoulos S, Goulis I, Cholongitas E. Pulmonary manifestations of chronic liver disease: A comprehensive review. *Ann Gastroenterol* 2020;33:237-49.
- Riou M, Jutant EM, Mignard X, Canuet M, Humbert M, Sitbon O. Hépatopathies et maladies vasculaires pulmonaires [Liver diseases and pulmonary vascular disorders]. *Rev Med Interne* 2018;39:925-34.
- Raevens S, Geerts A, Devisscher L, Van Vlierberghe H, Van Steenkiste C, Colle I. Recent advances in the approach to hepatopulmonary syndrome and portopulmonary hypertension. *Acta Gastroenterol Belg* 2021;84:95-9.
- Del Valle K, DuBrock HM. Hepatopulmonary syndrome and portopulmonary hypertension: Pulmonary vascular complications of liver disease. *Compr Physiol* 2021;11:1-22.
- Mallik M, Singhai A, Khadanga S, Ingle V. The significant morbidity and mortality indicators in patients of cirrhosis. *Cureus* 2022;14:e21226.
- Soulaidopoulos S, Cholongitas E, Giannakoulas G, Vlachou M, Goulis I. Review article: Update on current and emergent data on hepatopulmonary syndrome. *World J Gastroenterol* 2018;24:1285-98.
- Forde KA, Fallon MB, Krowka MJ, Sprys M, Goldberg DS, Krok KL, *et al.* Pulmonary vascular complications of liver disease 2 study group. pulse oximetry is insensitive for detection of hepatopulmonary syndrome in patients evaluated for liver transplantation. *Hepatology* 2019;69:270-81.
- Kennedy TC, Knudson RJ. Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. *Chest* 1977;72:305-9.
- Kumar P, Rao PN. Hepatopulmonary Syndrome. *N Engl J Med* 2020;382:e14.
- Fuhrmann V, Krowka M. Hepatopulmonary syndrome. *J Hepatol* 2018;69:744-5.
- Cywinski JB, Makarova N, Arney A, Liu Q, Fujiki M, Menon KVN, *et al.* Resources utilization after liver transplantation in patients with and without hepatopulmonary syndrome: Cleveland clinic experience. *Transplant Direct* 2020;6:e545.
- Sendra C, Carballo-Rubio V, Sousa JM. Hepatopulmonary syndrome and portopulmonary hypertension: Management in liver transplantation in the horizon 2020. *Transplant Proc* 2020;52:1503-6.
- Haj M, Rockey DC. Predictors of clinical outcomes in cirrhosis patients. *Curr Opin Gastroenterol* 2018;34:266-71.
- Benz F, Mohr R, Tacke F, Roderburg C. Pulmonary complications in patients with liver cirrhosis. *J Transl Int Med* 2020;8:150-8.
- Jose A, Shah SA, Anwar N, Jones CR, McCormack FX, Sherman KE, *et al.* Predictors of outcomes following liver transplant in hepatopulmonary syndrome: An OPTN database analysis. *Respir Med* 2021;190:106683.
- Parikh H, Lui E, Faughnan ME, Al-Hesayen A, Segovia S, Gupta S. Supine vs upright exercise in patients with hepatopulmonary syndrome and orthodeoxia: Study protocol for a randomized controlled crossover trial. *Trials* 2021;22:683.
- Marroni CA, Fleck AM Jr, Fernandes SA, Galant LH, Mucenic M, de Mattos Meine MH, *et al.* Liver transplantation

- and alcoholic liver disease: History, controversies, and considerations. *World J Gastroenterol* 2018;24:2785-805.
19. Marsico A, Dal Corso S, Carvalho EF, Arakelian V, Phillips S, Stirbulov R, *et al.* A more effective alternative to the 6-minute walk test for the assessment of functional capacity in patients with pulmonary hypertension. *Eur J Phys Rehabil Med* 2021;57:645-52.
  20. Roncato G, da Fontoura FF, Spilimbergo FB, Meyer GMB, Watte G, de Vargas WO, *et al.* Parasympathetic modulation withdrawal improves functional capacity in pulmonary arterial hypertension. *Respir Physiol Neurobiol* 2021;287:103620.
  21. Liu F, Tsang RCC, Jones AYM, Zhou M, Xue K, Chen M, *et al.* Cardiodynamic variables measured by impedance cardiography during a 6-minute walk test are reliable predictors of peak oxygen consumption in young healthy adults. *PLoS One* 2021;16:e0252219.