

Original Research Article

PREVALENCE AND RISK FACTORS OF HEPATOPULMONARY SYNDROME IN CHRONIC LIVER DISEASE: A CROSS-SECTIONAL ANALYSIS

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ABSTRACT

Background: Prevalence of hepatopulmonary syndrome and related clinical factors in chronic liver disease are not well defined, especially in tertiary care settings.

Materials and Methods: This cross-sectional observational study enrolled adults (≥ 18 years) with chronic liver disease and portal hypertension who showed $\text{SpO}_2 < 96\%$ or signs of HPS. Patients with major heart or lung diseases, lung cancer, or respiratory infection were excluded. HPS was diagnosed by pulmonary vascular dilation on imaging, portal hypertension, and hypoxemia ($\text{PaO}_2 < 80$ mmHg or $\text{A-aO}_2 \geq 15$ mmHg). The data collected encompassed clinical evaluations, laboratory findings, measures of liver severity (such as Child-Pugh and MELD scores), arterial blood gas analyses, and results from contrast echocardiography. Statistical methods applied included t-tests, Chi-square tests, Pearson correlations, ANOVA, logistic regression, and ROC curve analysis.

Results: Of 177 patients (mean age 60.5 years; male: female ratio 4.5:1), 14 (7.9%) had HPS, which was linked to more severe liver disease—higher Child-Pugh (12.5 vs 8.7, $P=0.001$) and MELD scores (23.9 vs 17.1, $P=0.001$). The A-aO_2 gradient correlated positively with both scores. Multivariate analysis showed HPS risk was higher in males, older individuals, and those with elevated A-aO_2 gradients. ROC analysis identified Child-Pugh > 10.5 and MELD > 18.5 as predictive cut-offs for HPS.

Conclusion: This study found an HPS prevalence of 7.9% among patients with chronic liver disease. Advanced age, male sex, and elevated A-aO_2 gradients were determined to be significant risk factors for the development of HPS. These findings underscore the importance of timely identification and assessment of HPS in individuals with chronic liver disease to optimise management strategies and improve patient outcomes.

Keywords: Chronic liver disease, Hepatopulmonary syndrome, Child Pugh score, Receiver operating characteristic curve, multivariate analyses.

INTRODUCTION

Cirrhosis and chronic liver disease are major global health concerns, mainly caused by hepatitis B, hepatitis C, alcohol-related liver disease, and metabolic dysfunction-associated steatohepatitis.^[1,2] Cirrhosis and portal hypertension alter blood flow and vascular balance, affecting pulmonary circulation. This can result in hepatopulmonary syndrome (HPS), which is frequently overlooked as

patients often have no symptoms or only mild ones like shortness of breath and fatigue.

HPS prevalence in liver disease patients ranges from 11% to 32%, varying by diagnostic criteria, patient population, and assessment methods. Data on HPS rates and features in chronic liver disease, especially in tertiary care settings, remain limited.^[3-5]

Several studies indicate that HPS may occasionally be associated with more severe chronic liver disease, as assessed by the Child-Pugh (CP) score or the

Model for End-Stage Liver Disease (MELD) score; yet not all research has confirmed this link.^[5,6]

Recent studies show that HPS progresses over time, leading to reduced survival in patients awaiting orthotopic liver transplantation and higher mortality after the procedure, mainly due to cardiorespiratory complications.^[7]

This study was undertaken to determine the prevalence of HPS among patients with chronic liver disease at a tertiary care teaching institute, and to evaluate the association of HPS with demographic and clinical parameters, including liver disease severity scores such as the Child-Pugh and MELD scores. By employing standard diagnostic modalities, including agitated saline contrast echocardiography and arterial blood gas analysis, the study aims to enhance understanding of HPS in this patient population, thereby informing early recognition and management strategies.

MATERIALS AND METHODS

A cross-sectional observational study was performed at a tertiary care teaching hospital between November 2023 and April 2025. Institutional Ethics Committee approval was obtained, and the trial was conducted in accordance with the tenets of the Declaration of Helsinki.

Inclusion criteria

Include all patients aged 18 or older diagnosed with chronic liver disease and portal hypertension. Eligibility extends to those with SpO₂ below 96% on room air or exhibiting signs such as clubbing, platypnoea, or other indicators of hepatopulmonary syndrome.

Exclusion criteria

Patients with underlying cardiovascular disease classified as New York Heart Association (NYHA) Functional Classification grade 2 or higher, as well as those with obstructive or restrictive respiratory diseases, were excluded from this study. Additionally, individuals presenting evidence of lung malignancy or respiratory tract infection were not included.

Diagnostic criteria for HPS: Pulmonary vascular dilation detected on lung-perfusion scan or contrast echocardiography; portal hypertension present. PaO₂ < 80 mmHg or A-aO₂ ≥ 15 mmHg on room air (A-aO₂ > 20 mmHg if over 64). A-aO₂ Gradient = [(FiO₂ × (760 – 47)) – (PaCO₂ / 0.8)] – PaO₂.

Data Collection: A comprehensive clinical history and examination will be conducted. Patients meeting the inclusion criteria will be identified. All participants will have liver cirrhosis confirmed through clinical evaluation, laboratory results, ultrasonography, liver elastography, and—when available—liver histology obtained via biopsy. Selected individuals will undergo standard investigations including liver function tests, complete blood count, serum albumin, and prothrombin time. Subsequently, the following scores will be

calculated: Model for End-Stage Liver Disease (MELD) and Child-Pugh Score.

Patients exhibiting an SpO₂ level below 96% on room air via pulse oximetry, or demonstrating clinical signs such as clubbing, platypnoea, or other indicators suggestive of hepatopulmonary syndrome, will undergo further screening. Additional assessments will include arterial blood gas analysis and agitated saline contrast-enhanced echocardiography to determine the prevalence of HPS among individuals with chronic liver disease. For patients diagnosed with HPS, the severity of their chronic liver disease will be evaluated accordingly.

Outcome measures: The main outcome was the prevalence of HPS in chronic liver disease patients, while the secondary outcome was the severity of liver disease in those with HPS.

Sample size calculation: The aim was to estimate the prevalence of unknown parameter(s) from the target population using a random sample. Sample size was calculated using formula,

$$N = Z^2 P (1-P) / d^2$$

In this formula, N is the sample size, Z is the statistic corresponding to level of confidence (standard normal variate), P is expected prevalence (that will be obtained from previous studies published or a pilot study conducted by the researchers in our region), and d is precision (corresponding to effect size). According to a recent study by El-Maraghy et al,^[8] the prevalence of HPS in patients with cirrhosis was 25.28%. Considering a precision error of 7%, the level of confidence aimed for was 95%, the normal standard variate Z=1.96, the estimated sample size was calculated to be 146.

Statistics: Statistical analysis was performed using IBM statistical software, SPSS Statistics version 30 (IBM Inc, Armonk, NY, USA). Data was checked for normality using Shapiro-Wilk test. Outliers were identified by visual inspection of boxplots. Descriptive statistics, including mean and standard deviation (SD), were calculated for all continuous variables, while frequencies and percentages were assessed for categorical variables. The independent-samples t-test was employed to evaluate differences between the means of two independent groups on a continuous dependent variable. Associations between categorical variables were analyzed using Chi-square tests.

The Pearson product-moment correlation was utilized to assess the strength and direction of linear relationships between continuous variables, generating a Pearson correlation coefficient (r), which ranges from -1 (indicating a perfect negative linear relationship) to +1 (indicating a perfect positive linear relationship). A coefficient value of 0 denotes no linear relationship between the variables. One-way ANOVA was performed to determine any statistically significant differences among the means of two or more independent groups, with a P value less than 0.05 considered statistically significant. A multivariate regression model was developed to identify factors associated with an increased

likelihood of HPS. Variables found to be significant in univariate analysis (gender, age, SPO₂, and A-aO₂ gradient) were included in this model. Receiver Operating Characteristic (ROC) curve analyses were conducted to evaluate the predictive capabilities of MELD and Child-Pugh scores for HPS and liver disease severity.

RESULTS

The mean participant age was 60.5±11.6 years (range 31–87). Of the group, 145 were male (male: female ratio 4.5:1). Females were significantly older than males (65.6±10.8 vs 59.4±11.6 years, $P=0.006$), while males had higher CP scores than females (9.2±2.5 vs 8.1±1.8, $P=0.022$).

Among the 177 patients evaluated, an elevated A-aO₂ gradient was identified in 114 individuals (64.4%). Agitated saline contrast echocardiography revealed intrapulmonary shunting in 15 patients (8.5%). Accordingly, the prevalence of hepatopulmonary syndrome (HPS) in this cohort was 14 patients (7.9%).

[Table 1] summarizes the demographic and clinical characteristics of the study population based on the presence or absence of HPS. Patients diagnosed with hepato-pulmonary syndrome (HPS) exhibited more advanced liver disease, as indicated by their significantly higher Child-Pugh (CP) and MELD scores. In this study, 40 patients (22.6%) were classified as Child-Pugh stage A, 61 patients (34.5%) as stage B, and 76 patients (42.9%) as stage C. HPS was much more common among patients in Child-Pugh class C (64.3%) than in class B (35.7%) or class A (0%), with a P -value of 0.049.

A-aO₂ gradient and Child-Pugh (CP) score

A statistically significant positive correlation was observed between the A-aO₂ gradient and CP score [Figure 1a], as indicated by Pearson's correlation coefficient ($r = 0.253$, $P < 0.001$).

A-aO₂ gradient and Model for End-Stage Liver Disease (MELD) score

A notable and favourable correlation was found between the A-aO₂ gradient and MELD score (see Figure 1b), with Pearson's correlation coefficient measured at $r = 0.229$ and a significance of $P < 0.001$.

Multivariate analysis: The logistic regression model was statistically significant, $\chi^2(8) = 10.679$, $p < .0005$. The model explained 24.8.0% (Nagelkerke R²) of the variance in HPS and correctly classified 92.1% of cases. Of the four predictor variables only one was statistically significant. Male gender (OR=1.038), higher age (odds ratio=1.146) and elevated A-aO₂ gradient (OR=1.2) had increased likelihood of developing HPS. Regression coefficients are mentioned in [Table 2].

ROC curve analysis: The area under the curve (Figure 2a) for Child-Pugh score was 0.916 (95% CI-0.860 to 0.972), $P<0.001$. Based on the coordinate points on the curve, sensitivity was 96% and

specificity was 83%, respectively. The cut-off for CP score was 10.50 for discriminating patients with HPS. The area under the curve (Figure 2b) for MELD was 0.795 (95% CI-0.688 to 0.903), $P<0.001$. Based on the coordinate points on the curve, sensitivity was 85% and specificity was 60%, respectively. The cut-off for MELD was 18.50 for discriminating against patients with HPS.

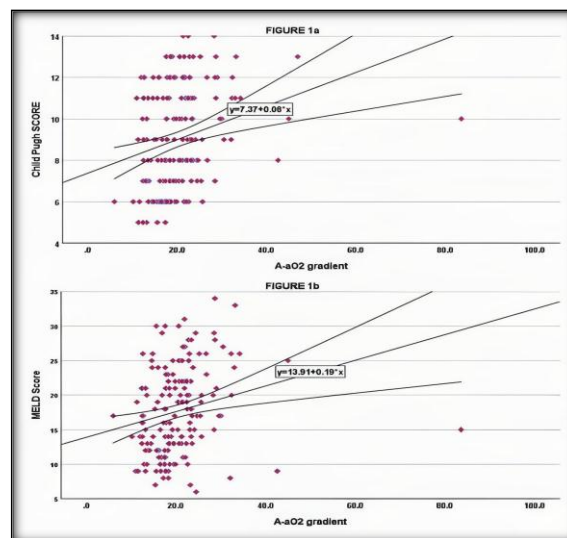


Figure 1: a illustrates a scatter plot that demonstrates a significant positive correlation between the A-aO₂ gradient and Child Pugh score, with Pearson's correlation coefficient $r=0.229$ and p -value <0.001 . Figure 1b displays a scatter plot showing a similar significant and positive relationship between the A-aO₂ gradient and MELD score, also with $r=0.229$ and $p<0.001$.

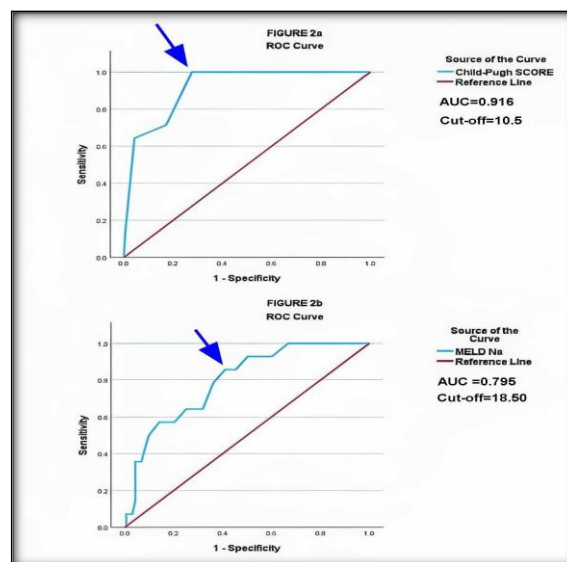


Figure 2: a shows a ROC curve for the Child-Pugh score with an area under the curve of 0.916 (95% CI: 0.860–0.972, $P<0.001$). Sensitivity was 96% and specificity was 83%. The cut-off CP score to distinguish patients with HPS was 10.50. Figure 2b presents a ROC curve with an AUC of 0.795 (95% CI: 0.688–0.903, $P<0.001$) for MELD. Sensitivity and specificity were 85% and 60%, respectively, at a cut-off of 18.50 for distinguishing patients with HPS.

Table 1: Demographic and clinical profile.

Variable	HPS present (n=14)	HPS Absent (n=163)	P value
*Age (years)	55.4±9.5	61±11.7	0.088
**Males	11(6.2)	134(75.7)	0.720
**Clinical findings			
Clubbing	8(4.5)	14(7.9)	<0.001
Platypnoea	4(2.2)	12(6.8)	0.026
*SpO2	93.3±2.4	94.1±1.6	0.077
*A-aO2 gradient	30.3±16.6	19.5±5.7	<0.001
*CP score	12.5±1	8.7±2.3	0.001
*MELD score	23.9±5.3	17.1 ±6	0.001

**Expressed as frequency and percentage, *Expressed as Mean±SD

Table 2: Variables in the equation

Parameter	B	SE	df	P value	Odds ratio	95% CI for OR	
Gender	0.037	0.891	1	0.967	1.038	0.181	5.951
Age	0.045	0.029	1	0.115	1.146	0.989	1.206
A-aO2 gradient	0.182	0.195	1	0.003	1.200	0.819	1.758
SpO2	-0.120	0.041	1	0.349	0.887	0.818	0.996
Constant	-14.532	18.762	1	0.439	0.000		

a. Variable(s) entered on step 1: GENDER, AGE, SPO2, A-aO2 gradient.

DISCUSSION

This prospective observational study investigated how common hepatopulmonary syndrome is among patients with chronic liver disease at a tertiary teaching hospital in southern India.

Our study found HPS prevalence was 7.9%. Patients with HPS had more severe liver disease, indicated by higher Child-Pugh and MELD scores. Multivariate analysis showed increased risk of HPS in males (OR=1.038), older age (OR=1.146), and elevated A-aO2 gradient (OR=1.2).

Hepatopulmonary syndrome (HPS) is characterized by a triad consisting of liver cirrhosis and/or portal hypertension, arterial deoxygenation, and intrapulmonary vascular dilatations (IPVD). Morphological changes in the lungs of individuals with advanced liver disease—such as increased number and dilation of pulmonary blood vessels—may impede efficient oxygen transport by erythrocytes. The severity of HPS is determined by partial pressure of arterial oxygen (PaO2), which can be assessed using arterial blood gas (ABG) analysis. HPS is often underdiagnosed because many patients show no symptoms or only mild complaints. However, dyspnoea, platypnea, spider nevi, cyanosis, and finger clubbing occur more frequently in HPS than in liver disease without HPS.^[8-10]

HPS prevalence in chronic liver disease varies between 4% and 47%, averaging 25%, depending on diagnostic methods and population.^[11,12] A prospective study by Schenk et al. (n=111) found a 24% prevalence in cirrhosis patients using specific diagnostic tests.¹³ In cirrhosis, HPS rates range from 4% to 30%, while in end-stage liver disease, prevalence is reported at 5% to 35%.^[14] A prospective study conducted by Younis et al., utilizing saline bubble echocardiography in patients with cirrhosis (n=110), reported a 26% prevalence of HPS.^[15] In comparison, our research, which employed agitated saline contrast-enhanced echocardiography, identified an HPS prevalence of

7.9%, falling within the established range for individuals with chronic liver disease.

Singhai et al studied 100 cirrhosis patients for over a year, using Child-Pugh and MELD scores to assess severity. All patients underwent contrast echocardiography, arterial blood gas tests, 6MWT, and chest imaging. Patients with HPS had higher MELD (29 vs. 22, P <.0001) and Child-Pugh scores (P=0.027). HPS prevalence was greater in Child-Pugh class C (64.3%) than in class B (35.7%) or A (0%) (P = 0.049).^[16]

Haj et al found a positive link between HPS and severe cirrhosis in ambulatory patients, using Child Pugh and MELD scores. Other studies have reported similar associations.^[17,18]

Khiangte et al. conducted a cross-sectional observational study at a tertiary care center involving patients with decompensated chronic liver disease who were admitted for pre-liver transplant evaluation. The authors observed that individuals with hepatopulmonary syndrome (HPS) exhibited more advanced liver disease. A MELD-Na score greater than 19 was found to be associated with HPS, demonstrating a sensitivity of 73.08%, specificity of 65.79%, positive predictive value (PPV) of 59.4%, and negative predictive value (NPV) of 78.1%. In our study, the MELD score cut-off was 18.50, which was comparable to this research; however, the sensitivity observed in our cohort was higher, at 85%.^[19]

Our study had several limitations and strength. This research was carried out at a single tertiary teaching hospital, which might limit how well its findings apply to other groups or settings. With only 177 patients included, the study provides useful insights, but its small size may not capture fewer common trends or fully represent all individuals with chronic liver disease from different regions.

Since this is a cross-sectional study, it cannot track changes over time or prove cause-and-effect relationships. Longer-term studies are required to assess how HPS impacts outcomes such as survival and transplantation. Although agitated saline contrast

echocardiography and arterial blood gas analysis were used to diagnose HPS—both standard methods—there are newer diagnostic tools that may be more sensitive or specific. Several possible confounding factors, like additional heart or lung diseases, medications, and lifestyle choices, were not thoroughly explored or controlled for, which could influence the observed results. No follow-up data were available regarding long-term patient outcomes, including survival rates, post-transplant results, or quality of life, making it harder to understand the true impact of HPS in chronic liver disease. Some clinical signs, such as platypnoea and clubbing, depended on physician assessments, raising potential issues of observer bias or differences in judgment.

CONCLUSION

In conclusion, this cross-sectional study at a tertiary care teaching hospital found that hepatopulmonary syndrome (HPS) occurred in 7.9% of patients with chronic liver disease. HPS was associated with more advanced liver disease, as indicated by higher Child-Pugh and MELD scores. Older age, male gender, and elevated A-aO₂ gradient increased the likelihood of developing HPS. The findings highlight the importance of early recognition and assessment for HPS in patients with chronic liver disease to improve management and outcomes.

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