

Incidence of Hepatopulmonary Syndrome in Cirrhosis of Liver

N BARLAS J AKRAM S ABAIDULLAH

Department of Medicine, K. E. Medical College/Mayo Hospital, Lahore
Correspondence to Dr. Nazeefa Barlas, e. mail: drnazeefa6@hotmail.com

Background: Patients of advanced liver cirrhosis regardless of the etiology may have coexistent hypoxemia, increased alveolar arterial oxygen gradient leading to hepatopulmonary syndrome which is documented by various techniques. **Aim:** To assess the incidence of HPS in 50 consecutive cirrhotic patients who presented to outpatients department or medical casualty. **Patients:** Patients of both gender, with ages between 12-70 years and belonged to any class of child's Pugh classification were included. **Results:** Male and female patients included in the study were of equal number among patients with HPS and without HPS. Among the HPS patients HBsAg was 46.15 as compared to 32.43 in patients without HPS. Similarly more number of patients who had both HBsAg and anti HCV belonged to HPS positive group (15.38) in comparison to only 10.81, who were HPS negative. Number of episodes of encephalopathy were found to be more (1.85) among HPS patients, and less (0.90) among HPS negative patients. Portal vein diameter (in cm) was also found to be increased (13.61) among HPS patients and 11.94 among patients without HPS. Biochemical parameters also depicted greater derangement among the HPS patients like bilirubin was 4.05 among HPS in comparison to 1.92 in patients without HPS. Albumin was less 2.55g/dl in HPS patients while it was 3.50 among HPS negative patients. Prothrombin time (sec) was also more prolonged (6.92 sec) among HPS patients while it was 3.27 among HPS negative patients. Hypoxemia was more (62.73mmO₂ partial pressure) among patients of HPS as compared to 79.24mmHg among patients without HPS. It was also noted that oxygen concentration was lowest in child's class C (66.47) and 72.2% cases of HPS belonged to the same class. While 0% cases of HPS were present among child's class a and b respectively. **Conclusion:** The incidence of HPS among our selected group of patients was found to be 26%. Hypoxemia worsened with the advancement of liver disease; oxygen concentration was 93.31±6.52, 83.58±7.58, 66.47±8.09 among child's class a, b and c respectively and the maximum HPS patients (72%) belonged to class C, in comparison to 0% among both child's class a and b.

Key words: Cirrhosis of liver, Hepatopulmonary syndrome, chronic liver disease

Chronic liver disease is common in Southeast Asia primarily due to high prevalence of chronic viral hepatitis¹. One of the recently described outcome of chronic liver disease is the development of porto pulmonary pressure changes which manifest as Hepatopulmonary Syndrome (HPS) The essentials to the diagnosis of this entity include documentation of cirrhosis of liver, arterial hypoxemia and increased alveolar-arterial oxygen gradient. It generally manifests in patients with advanced liver disease as dyspnoea, cyanosis, clubbing and platypnoea. None of these features are specific to this syndrome. It is necessary to exclude other possible etiologies for above mentioned manifestations like cardiopulmonary embarrassment due to chronic obstructive pulmonary disease (COPD), valvular heart lesions etc. The vasodilatory mediators like nitric oxide lead to pre and post capillary pulmonary dilatations which alter the blood flow patterns leading to hypoxemia².

These abnormal dilatations known as pulmonary spiders and angiomas are detected by various techniques including contrast enhanced angiography, macro aggregated albumin scan and contrast echocardiography preferably transesophageal route done by injecting agitated saline via peripheral vein and there is appearance of bubbles of left cardiac chambers^{3,4}. Coexistent hypoxemia is shown by arterial blood gas analysis of patient breathing room air establishes the diagnoses of hepato pulmonary syndrome. It is noted that incidence of HPS increases with increasing severity of underlying chronic liver disease (CLD)⁵. We planned this study to know the incidence of

hepatopulmonary syndrome in chronic liver disease in one of the highest prevalence areas and correlate the severity of syndrome with severity of liver disease.

Materials and methods

This prospective study was conducted in a tertiary care hospital on 50 consecutive patients of decompensated cirrhosis who presented through out patients and accidents/emergency department. The inclusion and exclusion criterion were as follows:

Inclusion Criteria

1. Consecutive patients of liver cirrhosis presenting to out patients department or medical casualty were included.
2. Primary criteria of inclusion was the presence of liver cirrhosis without any selection bias and irrespective of the presence or absence of a history of dyspnoea or cyanosis on physical examination.
3. All the patients of cirrhosis of liver irrespective of the etiology of cirrhosis were entertained.
4. Both male and female patients were included.
5. Ages of the selected patients were between 12-70 years as beyond this age group physiological changes in pulmonary system widens the alveolar arterial oxygen gap.
6. Patients could be suffering from any degree of severity of liver disease according to child's Pugh classification.

Exclusion Criteria

Patients with significant concomitant disease that could alter the results of Arterial Blood Gases (ABG'S) or echocardiography were excluded from the study such conditions could be:

- a. Congestive cardiac failure due to some other disease e.g., diabetes mellitus, valvular heart disease etc.
 - b. Any patient with cardiac shunts obvious on echocardiography.
 - c. COPD or interstitial lung disease diagnosed on history, physical examination and chest x-ray.
 - d. Patients did not smoke heavily in proceeding 2 weeks, as oxygen concentration could alter.
 - e. Advance renal failure cases, whether acute or chronic were also excluded.
 - f. Patients who were currently suffering from lower respiratory infections e.g., Lobar or bronchopneumonia diagnosed on history physical examination and chest x-ray were excluded.
 - g. Patients with plural effusion were also not included as it could alter ABG'S.
 - h. Patients with tense ascites which altered the diaphragmatic movements and could lead to hypoxemic changes in ABG'S were not included.
2. Patients who bled acutely or with hemodynamic instability were excluded, or
3. Patients who were taking vasoconstrictor or vasodilator therapies.

Patients who met abovementioned criteria were provided with the full insight of the methodology of the study and informed consent was obtained. A detailed history was taken and general physical examination was done. Examination relevant to CLD was done. The following points were particularly noted: spider angiomata, jaundice ascites, hepatic flap, encephalopathy, skin and nail changes. Laboratory features: viral serology for hepatitis B & C by ELISA, blood complete examination, prothrombin time (PT), serum albumin/liver function tests (LFT'S). Severity of liver disease was graded by child's Pugh classification.

The study was carried out by injecting 10 cc normal saline which was agitated prior to intravenous administration. Transthoracic echocardiography was done to obtain apical four chamber view, with probe frequency specification of 2.5-5HZ, (G.E.RT.6800-MODEL N046-285282G5). Person doing echocardiography was blinded to the patient's clinical data.

The opacification grades of echocardiography were described by Williams E Hopkins et al in 1990⁶. The grades are as follows:

- Grade 0: No appearance of contrast in left atrium/ventricle.
- Grade 1: A few microbubbles occupying less than half of left atrial cavity on visual impression.
- Grade 2: Microbubbles occupying more than half to whole of left atrial cavity but less dense than right atrial cavity.

Normally these microbubbles introduced peripherally are absorbed in capillaries of lungs. Unless there is existence of pre and post capillary dilatations(>15um). In HPS there are dilatations of the capillaries due to the effect of various mediators and microbubbles introduced appear on right side of heart after 3-6 cardiac cycles. Arterial blood gas estimation was done according to the standardized protocol⁷.

Results

Table 1 shows the demographic variables of the study population in which age, was less among HPS negative cases as compared to HPS positive patients with a p value of 0.14. Although male and female were almost equal in number among the two groups. As far as the etiology is concerned it was seen that HBsAg earlier patients were in greater number than the negative cases while anti HCV positive cases were more among patients who did not have HPS while patients positive for both markers were more among HPS positive cases.

Table 1: Demographic variable of study population

Demographic features	HPS present	HPS absent	P value
Age	57.07	50.32±13.67	0.14
Sex	Male: 9 Female: 7	Male: 8 Female: 7	
HbsAG	46.15	32.43	
Anti HCV	53.84	59.45	
Both	15.38	10.81	

Table 2 shows the comparison of clinical and biochemical characteristics among HPS positive and HPS negative patient in this study. Among the clinical parameters number of episodes of encephalopathy were noted to be more (1.857) in patients who were HPS positive while HPS negative patients had much less number of such episodes. Similarly other clinical characteristics depicting severity of chronic liver disease such as splenomegaly and portal vein diameter also showed P value which was statistically significant among HPS positive patients. However the grade of ascites showed P value 0.01 among HPS positive and negative cases.

When biochemical parameters were considered it was seen that liver functions like bilirubin, SGOT, SGPT, albumin and PT were much more deranged in HPS positive cases. The oxygen partial pressure was 62.73 and 79.24 among HPS positive and negative cases respectively.

Table 3 compares various parameters of severity of liver disease between patients having full syndrome of HPS and patients who had contrast positivity but oxygen partial pressure greater than 70 mmHg. It can be seen that it is only with advanced liver disease that oxygen partial pressure drops in arterial blood while shunt may still be documented relatively easily.

Table 2: Severity of liver disease in patients with and without HPS

Clinical parameters	HPS	HPS	P value
	present	absent	
Encephalopathy (No. of episode)	1.85	0.90	0.10
Splenomegaly (cm)	15.70	15.30	0.59
Ascites (grade)	2.31	1.62	0.01
Portal vein (cm)	13.61	11.94	0.09
Biochemical parameters			
Bilirubin (mg/dl)	4.05	1.92	0.06
Albumin (g/dl)	2.55	3.50	0.018
PT prolongation (sec)	6.92	3.27	0.002
APTT Prolongation (sec)	4.47	6.08	0.013
ALT (mg/dl)	39.89	33.35	0.322
AST (mg/dl)	35.90	42.75	0.61
O2 partial pressure (mmHg)	62.73	79.24	0.00

APTT Prolongation (in seconds) of patients Vs control

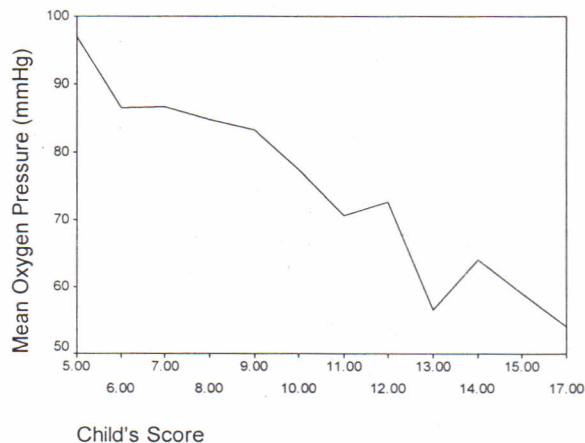
PT Prolongation (in seconds) of patients Vs control

AST Aspirate aminotransferase

ACT Alanine aminotransferase

Table 3. Incidence of echocontrast positivity and hepatopulmonary syndrome according to severity of liver disease.

Child's class	O ₂ concentration (mean)	Echocontrast positive (%)	HPS positive (%)
a	93.31±6.52	10	0
b	83.58±7.58	31	0
c	66.47±8.09	100	72.2



Discussion

HPS is defined as triad of chronic liver disease, arterial hypoxaemia and presence of intrapulmonary vascular dilatations. The biochemical mediators due to altered liver function result in changes in various vascular beds and lead to formation of spider nevi, telengectasias, and manifest as cyanosis and palmar erythema. Such vascular dilatations and arteriovenous shunts can lead to arterial hypoxemia when severe their presence can be documented in various ways. One such technique is contrast

echocardiography used in this study. HPS is not a new but a well recognized entity. Recent literature describes a high prevalence of HPS (5-29%) in advanced cirrhosis of liver. Our study was conducted in a tertiary care centre on a group of 50 patients with chronic liver disease. The overall incidence of HPS in this study was found to be 26%.

The severity of underlying liver disease was classified further on the basis of child's classification. The incidence of HPS was seen to be increasing with the severity of liver disease. As far as the etiology was concerned viral hepatitis B and C were the major contributors to the liver disease in our selected group of patients. It was seen that 41.7% cases had HBsAg and 58.82% cases were anti HCV positive, while 11.76% were positive for both viral markers. The overall contrast positive cases were 68%.

The etiology of cirrhosis among HPS and contrast positive cases had been studied by Hopkin A in a set of 53 patients. He found 25% cases had hepatitis C and 4% were HBsAg positive. He reported contrast positivity by echocardiography in 47% of cases. As far as the hypoxaemia is concerned he found no difference of mean partial oxygen (PaO₂) between echocontrast positive and negative groups. Significant lower arterial oxygen pressure (66±3mmHg) was found in patients of grade 2 to 4 contrast positivity⁷. However in our group of patients the mean oxygen concentration of contrast positive cases 72.2±9.81 and contrast negative cases was 93.05±5.49. Patients in child's class C had lowest concentration (66.47mmHg) as compared to those in class a and b who had oxygen concentration of 93.31mmHg and 83.58mmHg respectively. This relationship of Pugh's Score and hypoxemia was seen in 30 alcoholic cirrhotics who were assessed for the frequency of hypoxaemia and its relationship to liver failure by Roblero JP et al in Spain⁸.

The relationship of hypoxaemia with decompensation of liver function was also studied by S. Moller et al at Denmark where 142 patients with cirrhosis but without encephalopathy distributed according to child's classification were compared with 21 patients with encephalopathy. The prevalence of arterial hypoxaemia in cirrhotics was 22% among those without encephalopathy but it varied from 10-40% depending upon degree of hepatic dysfunction⁹.

In our study it was seen that child's class a and b had 0% incidence of HPS whereas it was 72.2% among the child's class c group of patients showing the decompensated liver functions had a clear rise in HPS. Such a similar finding was noted in Serbia Belgrade where 50 patients were studied. Among them 16(32%) were in child's a, 20(40%) in child's b and 14(28%) in class c¹⁰. HPS was diagnosed in 9(18%) patients with liver cirrhosis and majority of such cases of HPS belonged to child's class b and c.

The number of episodes of encephalopathy, ascited and liver functions like PT, serum albumin, serum

bilirubin were of much advanced degree among the HPS positive cases in our study.

Conclusion

The study concludes HPS defined by current criterion is common in advanced liver disease and should be looked for in microvascular dilatations in lungs as documented by macroaggregated albumin scan, contrast enhanced transthoracic echocardiography which starts much earlier in relatively mild liver disease and not necessarily be associated with hypoxemia and thus may not be of functional significance however it may be a marker of those who ultimately develop HPS.

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