Frequency of Hepatopulmonary Syndrome in Cirrhotic Patients
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ABSTRACT
Objective: To determine the frequency of Hepatopulmonary Syndrome (HPS) in patients with cirrhosis of the liver.
Study Design: Observational cross-sectional study.
Place and Duration of Study: Department of Gastroenterology and Hepatology, Shaikh Zayed Hospital, Lahore, from April 2005 to March 2006.
Patients and Methods: Fifty consecutive patients admitted with liver cirrhosis were recruited. Twelve patients were excluded due to inadequate echocardiography image quality and inability to perform lung function tests. The diagnosis of cirrhosis was made on clinical, biochemical, serological and metabolic workup, ultrasound abdomen or liver biopsy. Complete blood count, liver function tests, prothrombin time, serum albumin, echocardiography, chest radiograph, transthoracic contrast echocardiography, arterial blood gas analysis and pulmonary function tests (FEV1) were performed. Results were analyzed as percentages. Chi-square test of proportions and t-test were applied.
Results: Total patients evaluated were 38. Mean age was 47.92 ±11.38 years, with male (68.4%) to female (31.6%) ratio of 2.1:1. The commonest cause of cirrhosis was hepatitis C (71.1%). Out of the 36 patients, 11 (29.7%) had HPS including 5 (13.1%) with overt HPS and 6 (16.7%) with subclinical HPS. All patients with HPS had hepatitis C with Child-Pugh-Turcotte (CPT) class C. Factors associated with HPS were digital clubbing, arterial hypoxemia and intrapulmonary vascular dilatations (p=0.02, 0.05 and 0.000 respectively).
Conclusion: In this study, 28.9% patients with cirrhosis of the liver had HPS. All belonged to child class C due to hepatitis C. Digital Clubbing, arterial hypoxemia and intrapulmonary vascular dilatations were important features of hepatopulmonary syndrome.

Key words: Hepatopulmonary syndrome. Hepatic cirrhosis. Intrapulmonary vascular dilatations. Hepatitis C.

INTRODUCTION
Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages at which point the only option may be liver transplantation. Patients with cirrhosis are susceptible to a variety of complications. The Hepatopulmonary Syndrome (HPS), a complication of cirrhosis liver, is considered to be present in patients with the triad of liver disease, arterial hypoxemia or increased alveolar-arterial gradient, while breathing room air and evidence for intrapulmonary vascular abnormalities, referred to as Intrapulmonary Vascular Dilatations (IPVDs).
Prevalence of hepatopulmonary syndrome among patients with chronic liver disease ranges from 4 to 47%, depending upon the diagnostic criteria and methods used. Most patients present with signs and symptoms of liver disease, while pulmonary manifestations include cyanosis, dyspnoea, platypnoea, orthodeoxia and digital clubbing. Spider nevi are proposed as a cutaneous marker of intrapulmonary vascular dilatations.
Cirrhotic patients without HPS may have hypoxemia due to various reasons like ascites, diaphragmatic elevation and ventilation/perfusion mismatch. It is estimated that 45 to 69% of all patients with cirrhosis have at least mild hypoxemia. However, severe hypoxemia (PaO₂ <60 mmHg) is less common and in the absence of associated cardiopulmonary disease, should strongly suggest HPS.
In Pakistan, published data on this subject is scanty, perhaps due to the lack of diagnostic facilities. Early diagnosis is important in these cases so as to consider liver transplantation. Therefore, this study was planned to determine the frequency of hepatopulmonary syndrome in cirrhotic patients.

PATIENTS AND METHODS
It was an observational cross-sectional study. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from each patient. Non-probability purposive sampling technique was used. Fifty consecutive patients with cirrhosis of the liver admitted in the Department of Gastroenterology and Hepatology, Shaikh Zayed Hospital, Lahore, from April 2005 to March 2006 were
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Included. Patients with portosystemic encephalopathy grade II or above, poor echocardiographic image on contrast echocardiogram, unable to undergo pulmonary functions tests and patients with FEV1 < 66% of predicted value on pulmonary function testing, were excluded from the study.

Diagnosis of cirrhosis of the liver was made on clinical, biochemical, serological, ultrasound or liver biopsy findings. Presence of palmar erythema, leukonychia, clubbing, spider angiomas, gynaecomastia, testicular atrophy, ascites, splenomegaly and portosystemic collaterals along with serum albumin <3.5 gm/dl, prothrombin time prolonged > 3 seconds from control, and on ultrasound abdomen, findings of coarse echotexture, +/- nodular surface with irregular margins, the ratio of transverse caudate lobe to transverse right lobe width > 0.65,13 splenomagaly, ascites and portal vein diameter > 12 mm suggested liver cirrhosis.

The diagnosis of hepatopulmonary syndrome was based upon arterial hypoxemia, defined by a reduced partial pressure of arterial oxygen (PaO2 ≤ 70 mmHg) and detection of intrapulmonary vascular dilatations on two dimensional contrast echocardiography in patients with cirrhosis of the liver.14 The diagnosis of sub-clinical hepatopulmonary syndrome was made if the patients had intrapulmonary vascular dilatations on contrast echocardiography but PaO2 on arterial blood gas analysis was found to be > 70 mmHg.14,15 Detail history and thorough physical examination was done. Complete blood counts with Prothrombin Time (PT) and activated Partial Thromboplastin Time (APTT), liver function tests, serum albumin, electrocardiography, chest radiography, transthoracic contrast echocardiography, arterial blood gas analysis and pulmonary function tests were performed. Echocardiography was done (Toshiba-Aplio MCM 1754TS-Japan) by a consultant cardiologist in the department of cardiology. Ten millilitres agitated saline was used as a contrast medium, which created a stream of microbubbles after intravenous injection. In healthy individuals, these microbubbles, greater than 15 micrometer in diameter, opacify the right heart chambers only because they are filtered in the capillary bed and do not appear in the left side of the heart. The distinction between intrapulmonary or intracardiac shunt was made by the time of appearance of the microbubbles in the left heart chambers; in intracardiac shunt, the microbubbles appeared generally within three heartbeats after appearance in the right heart chambers and in the intrapulmonary shunt, they appeared 4-6 heartbeats after their initial appearance in the right side of the heart.11 Arterial blood gas samples were obtained in heparinised five millilitre syringe by percutaneous radial artery puncture with the subject in a seated position breathing room air, and were analysed immediately with a standard blood gas analyser (Blood Gas and Electrolyte Analyser-M348-Bayer Diagnostic). Lung functions were obtained using a computerised lung function machine (Schiller SP-10) according to standard procedures.16

Statistical analysis was performed using (SPSS 11.0.1). The qualitative variables were presented as frequency and percentages. The quantitative variables; partial pressure of oxygen (PaO2), CPT score and age were recorded as mean ± standard deviation. Comparison of frequencies and mean difference was done with chi-square test and t-test respectively. P-value <0.05 was considered significant.

RESULTS

A total of 38 patients were evaluated. Age ranged from 22-70 years (mean age 47.92 ±11.38 years) with male to female ratio 2.1:1 (26:12). Twenty seven patients (71.7%) had cirrhosis due to hepatitis C, 1 (2.6%) due to hepatitis B, 3 (7.9%) due to both hepatitis B and C and 7 (18.4%) had negative viral serology. Intrapulmonary vascular dilatations on contrast echocardiography were detected in 11 (28.9%) cases. Arterial hypoxemia PaO2 ≤ 70 mmHg was found in 8 (21.05%) cases. Out of 38 patients, 5 (13.2%) fulfilled the criteria for overt HPS. All 5 patients with overt HPS were due to hepatitis C with Child-Pugh-Turcotte class C and mean Child-Pugh-Turcotte score was 9.8 ±1.30. Mean PaO2 in patients with HPS was 60.80 ± 5.93. On comparing the groups of patients with HPS and without HPS, digital clubbing (p=0.02), arterial hypoxemia (p=0.000) and intrapulmonary vascular dilatations (p=0.000) on contrast echocardiography were statistically more prevalent in patients with HPS. Six (15.8%) patients had subclinical HPS. Three had arterial hypoxemia with PaO2≤70 mmHg but IPVDs on contrast echocardiography were not seen. The demographic, clinical and laboratory features of patients with HPS, and without HPS are compared in Table I.

Six were excluded because of portosystemic encephalopathy grade II or above, 3 had poor echocardiographic image on contrast echocardiogram and were excluded. Two patients were unable to undergo pulmonary functions tests and one had FEV1 < 66% of predicted value on pulmonary function testing, and was, therefore, excluded from the study.

DISCUSSION

In this study, the frequency of the overt HPS was 13.05%. This frequency of HPS, while using PaO2 ≤ 70 mmHg as a cut off value, is within the reported range of 4-47%.1-6 Rolla et al.17 and Aller et al.16 used saline solution for contrast echocardiography as used in this study. The frequency of HPS in those studies was 26.6 and 22% respectively. This difference in frequency of HPS may be...
due to the different criteria used for the diagnosis of HPS. Schenk and colleagues showed that by changing the cut off values of \( \text{PaO}_2 \) 70-60 mmHg, the frequency of HPS also changes from 15 to 12% respectively. 14

The frequency of intrapulmonary vascular dilatations measured by transthoracic contrast echocardiography in those patients was 11 (28.9%), within the 5-47% rate reported in the literature.15,17 The positivity of contrast echocardiogram in patients without hypoxemia was found to be 15.78%. An anatomically detected shunt has a physiological mismatch. Some authors suggest that the positivity in patients without hypoxemia may be due to shunts, which are not adjacent to the gas exchange area, a portopulmonary shunt or pleural vascular dilatations. None of these abnormalities cause hypoxemia alone; they produce positive contrast-echocardiography findings.3,18-20 Interestingly, 3 hypoxemic patients (7.89%) in this study had a negative contrast-echocardiogram. Pulmonary hypertension should be excluded in hypoxemia cases with negative contrast-echocardiography.21 In this study, no patient had clinical features suggestive of pulmonary hypertension.

Studies have shown association between HPS, central cyanosis and clubbing and spider nevi.22 The same results except spider angiomas were observed in this study. It has been suggested that spider nevi are important clinical finding in HPS but other researchers failed to confirm this finding.23 In this study, only 1 (20%) patient had spider nevi. This is perhaps due to the fact that the local cirrhotic patients usually have dark skin and the detection of cutaneous spider angiomas is difficult.

Conflicting data exist in the literature regarding the correlation between HPS and the severity of liver disease.25 Abrams et al. showed significantly lower \( \text{PaO}_2 \) values in Child-Pugh A cirrhosis compared with Child-Pugh B and C classes. Vachiery et al. showed that hypoxemic cirrhotics had a significantly higher CPT score. The study clearly showed a significant relation between the severity of HPS and CPT score.

Patients with subclinical HPS have potential risk of developing "clinically significant" HPS during the course of their disease but the risk is unknown and should be determined in a prospective follow-up studies.26,27 Previous studies showed that the most common underlying etiologies of HPS were cryptogenic cirrhosis and cirrhosis due to hepatitis B.28,29 But in this study, all patients with HPS had hepatitis C. This difference can be explained by the fact that hepatitis C is the commonest cause of hepatic cirrhosis in Pakistan.30

Limitations of this study are; small number of patients and single centre study.

### CONCLUSION

In this study, 11(40.7%) patients were found to have hepatopulmonary syndrome. There were no significant differences in demographic or clinical features compared with patients without hepatopulmonary syndrome, with the exception of hepatitis C with child class C, clubbing and oxygenation abnormalities.

### REFERENCES


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