ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 04, 2024

PREVALENCE OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER

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ABSTRACT

INTRODUCTION

Liver cirrhosis is a chronic illness encountered both at primary and tertiary care level. Development of lung manifestations in cirrhosis has several clinical repercussions because they carry a poor prognosis. These include pleural effusion, obstructive and restrictive lung disease, hepatopulmonary syndrome (HPS) and portopulmonary syndrome. HPS is a triad of hypoxemia, liver disease and intrapulmonary vascular dilatation. The prevalence of HPS in cirrhosis has been reported between 4-19%.

AIMS & OBJECTIVES

1. To detect the prevalence of HPS among cirrhotic patients.
2. To correlate severity of HPS with Child-Pugh class.
3. To study the clinical spectrum of HPS in cirrhotic patients.

MATERIAL & METHODS

Patients presented in Outpatient / Inpatient department of Gastroenterology in MM department institute of Medical sciences Mullana, Ambala with characteristic signs and symptoms of cirrhosis fulfilling the inclusion and exclusion criteria were included in the study. Data was collected in a pretested proforma and 120 cases were selected using simple random sampling technique. Patients were investigated for pulse oximetry or arterial blood gas analysis and contrast Echocardiogram. Appropriate statistical tests were applied.

RESULTS

In our study, Cirrhosis of liver was more commonly seen in middle aged adults (in 5th decade) with male to female ratio of 5:1. The most common complaint was abdominal distension among all study population. Grade II esophageal varices were the most common endoscopic finding. HPS was present in 10 patients (8.3 %). Clubbing, splenomegaly and orthodeoxia were observed in all patients of HPS. Among all classes of Child Pugh score, HPS was most commonly seen in class C.

There was a significant correlation between the HPS and Child – Pugh class and also between “subclinical” HPS and Child –Pugh class.

CONCLUSION

There was a significant correlation between HPS with Child –Pugh which signifies that more likelihood of developing HPS in advanced CLD patients. There is a need for requirement of early testing to rule out subclinical HPS and HPS in early stages of CLD to prevent mortality and morbidity.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 04, 2024

KEYWORDS
Hepatopulmonary syndrome, Hypoxemia, Orthodeoxia, Contrast echocardiogram.

INTRODUCTION

Cirrhosis is a stage of progressive, irreversible injury to hepatocytes leading to inflammation and fibrosis.[1] Cirrhosis can be compensated i.e. early stage or decompensated i.e. delayed stage, both of which differ in clinical features and prognosis.[2]

In the compensated cirrhosis there is no ascites, hyperbilirubinemia, hepatic encephalopathy and upper gastrointestinal (GI) bleed due to variceal rupture [2] but with decompensated cirrhosis, patients develop serious life-threatening complications like ascites, hyperbilirubinemia, hepatic encephalopathy, upper GI bleed due to variceal rupture. The median survival of patients with compensated cirrhosis and decompensated cirrhosis are 6.5 years and 2.5 years respectively.[2]

Portal hypertension and hyperdynamic circulation are the major reason of morbidity and mortality in liver cirrhosis. Portal hypertension develops as a consequence of fibrosis and vascular changes in hepatic parenchyma and systematically, respectively leading to collateral circulation formation and hyperdynamic circulation.[3]

The etiology of cirrhosis varies according to region being alcohol, chronic hepatitis B /C and NAFLD and NAFLD be the most common causes in western countries.[4,5,6] In United States, with a prevalence of NAFLD as cause is high as 30% in the general population[5]. whereas chronic hepatitis B is the primary cause of liver cirrhosis in the Asia-Pacific region.[7] Liver cirrhosis may be caused by inherited diseases such as hemochromatosis and Wilson's disease[8], autoimmune hepatitis.[9] and primary biliary cirrhosis, primary sclerosing cholangitis.[10]

Major complication of portal hypertension are ascites which is most commonly seen in decompensated cirrhosis and 5% to 10% of patients with compensated cirrhosis per year, variceal bleeding, hepatocellular carcinoma, hepatic encephalopathy, hepatic hydrothorax, hepatopulmonary syndrome (HPS), portopulmonary hypertension. [11]

The association of chronic liver disease with respiratory symptoms and hypoxia is well recognised, four main pulmonary complications that may occur in patients with chronic liver disease are pneumonia, hepatic hydrothorax, HPS and portopulmonary hypertension. [11]

HPS is defined as a disorder in pulmonary oxygenation, caused by intrapulmonary vasodilatation and, less commonly, by pleural and pulmonary arteriovenous communications occurring in cirrhosis of liver with portal hypertension.[12 ,13]

Worldwide, prevalence of HPS has been reported in about 10% of patients with chronic viral hepatitis in 15–23% of those with cirrhosis and in 28% of those with Budd-Chiari syndrome.[14]In cirrhotic patients who undergo LT evaluation HPS ranges from 5–32%[15] and intrapulmonary vascular dilatation (IPVD) without presence of classic triad of HPS can be detected by echocardiography in 50–60% of cirrhosis patients.[15] The clinical manifestations of HPS in patients with cirrhosis are dyspnoea and platypnoea in majority. Dyspnoea is the most common respiratory complaint in patients with HPS, but it is non-specific.[16]

There is no clear effective medical therapy for HPS, but liver transplantation (LT) has shown to improve survival even in patients with severe disease.[17]

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AIM OF THE STUDY

1. To detect the prevalence of hepatopulmonary syndrome (HPS) among cirrhotic patients.
2. To correlate severity of HPS with Child-Pugh class.
3. To study the clinical spectrum of HPS in cirrhotic patients.

MATERIAL AND METHODS

This was an observational study carried out in MMIMSR, Mullana, Ambala. A total of 120 cases were included in the study from outpatient / inpatient Department of Gastroenterology in MM department institute of Medical sciences Mullana, Ambala during the period of 2021 to 2023.

Study Methodology

Patients presenting with characteristic signs and symptoms of cirrhosis coming to Department of Gastroenterology OPD / IPD were included in the study. Demographic information, symptoms, and clinical signs of patients were recorded on pre-designed structured proforma. Cirrhotic patients were graded as Child A, B, and C classes based on Child–Pugh classification.

History / physical examination

↓

CBC / LFT / RFT / PT-INR / VIRAL MARKERS

↓

Abdominal USG & Chest X-Ray

↓

Measurement of SpO2 by pulse oximeter or ABG

↓

Contrast enhanced Echocardiography

INCLUSION CRITERIA

Patient with evidence of cirrhosis of liver by -

1) Clinical findings.
2) Biochemical parameters.

EXCLUSION CRITERIA

1) Patients with coexisting primary pulmonary disease like COPD, Bronchial asthma, ILD.
2) Coexisting intracardiac shunts including patent Foramen Ovale (PFO).
3) History of smoking

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4) EHPVO (extra hepatic portal vein obstruction)

Echocardiogram:

A 2-D transthoracic contrast enhanced echocardiography was done for all patients. Contrast-enhanced echocardiography with agitated saline was done to detect pulmonary vascular dilatation and shunts.10ml of agitated solution of normal saline was administered to all the patients in the supine position. A positive test was defined as any visualization of microbubbles in the left heart chambers after three cardiac cycles after its appearance in the right ventricle in any of three injections.[18]

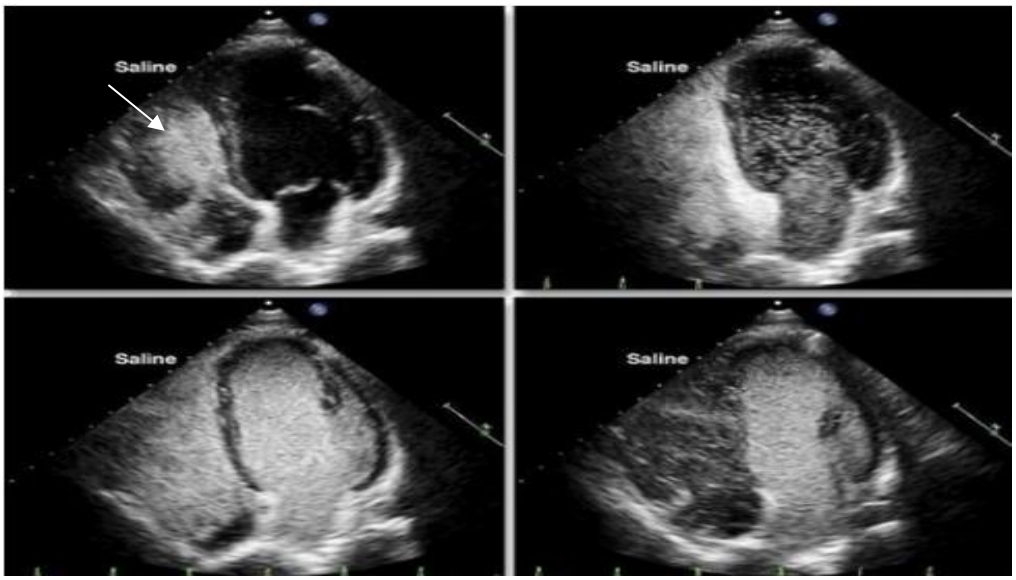

Figure 1: 2-D transthoracic contrast enhanced echocardiography showing microbubbles in the left heart chambers(arrow) after three cardiac cycles after its appearance in the right ventricle in any of three injections.[18]

Statistical Analysis:

All statistical analysis were performed using SPSS software (version **21, SPSS** Inc, Chicago, IL). Correlation between the variables will be estimated using correlation coefficient (r). P value of < 0.05 will be considered significant for the analysis.

RESULTS

Majority of study subjects of cirrhosis (52 patients) belonged to the age group of 51-60 years (43.4 %). The mean age of subjects was 48 $\pm$ 10.69 years. Among 120 patients included in our study, 103 patients (85.8 %) were males and 17 patients (14.2 %) were females. In our study, the most common cause for cirrhosis was alcohol, seen in 72 patients (60%) followed by hepatitis B (7.5 %), hepatitis C (5 %). (Table 1)

In our study, abdominal distension was the most common presenting symptom present in 83 patients (69.2%), followed by swelling of legs in 74 patients (61.7%). The most common respiratory symptom was breathlessness present in 67 patients (55.8 %) followed by cough in 14 patients (11.6 %). In our study, pallor was seen in 96 patients (80%) and splenomegaly was seen in 96 patients (80%) followed by ascites in 90 patients (75%) and bilateral pedal edema in 74 patients (61.7 %). Icterus was seen in 65 patients (54.2%), spider naevi in 24 patients (20 %) were the signs present in among all studied subjects. (Table 1)

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Table 1: Demographic and Clinical Characteristics of the Study subjects

Characteristic	Frequency (n=120)	Percentage (%)
Age group (years)		
20 - 30	3	2.5
31- 40	25	20.8
41-50	28	23.3
51-60	52	43.4
>60	12	10
Gender		
Male	103	85.8
Female	17	14.2
Etiology		
Alcohol	72	60
Hepatitis B virus	9	7.5
Hepatitis C virus	6	5
Others	33	27.5
Chief complaints		
Abdominal Distension	83	69.2
Swelling Of Legs	74	61.7
Breathlessness	67	55.8
Yellowish Discoloration of Eyes and Skin	63	52.5
Cough	14	11.6
Fever	12	10
Clinical Signs		
Pallor	96	80
Splenomegaly	96	80
Ascites	90	75
Pedal Edema	74	61.7
Icterus	65	54.2
Spiner Naevi	24	20
Clubbing	17	14.2
Cyanosis	12	10
Orthodeoxia	10	8.3

Among HPS patients abdominal distension was the most common presenting symptom, present in 9 patients (90 %) followed by breathlessness in 8 patients (80 %) , yellowish discoloration of eyes and skin in 8 patients (80 %). In our study, clubbing, splenomegaly and orthodeoxia were seen all patients having HPS. Pallor, ascites and spider naevi were seen in 9 patients (90 %) among HPS cases. (Table 2)

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Table 2: Clinical spectrum among HPS cases

Characteristic	Frequency (n=10)	Percentage (%)
Chief Complaints		
Abdominal Distension	9	90
Breathlessness	8	80
Yellowish Discoloration Of Eyes And Skin	8	80
Swelling of Legs	7	70
Cough	1	10
Fever	0	0
Clinical Signs		
Orthodeoxia	10	100
Clubbing	10	100
Splenomegaly	10	100
Pallor	9	90
Ascites	9	90
Spiner Naevi	9	90
Icterus	8	80
Pedal Edema	7	70
Cyanosis	5	50

In our study, 20 patients (16.6 %) showed grade 1 varices, 74 patients (61.6 %) showed grade 2 varices and 26 patients (21.8 %) showed grade 3 varices. In our study of 120 cirrhotic patients, IPS (intrapulmonary shuts) was present in 43 patients (35.8%). In our study of 120 cirrhotic patients, 24 patients (20%) were in Child- Pugh class A, 60 patients (50%) were in Child-Pugh class B and 36 patients (30%) were in Child-Pugh class C. In our study of 120 cirrhotic patients, hepatopulmonary syndrome was present in 10 patients (8.3%). (Table 3)

Table 3: Clinical Examination Characteristics of the Study subjects

Characteristic	Frequency (n=120)	Percentage (%)
Esophageal varices		
Grade 1	20	16.6
Grade 2	74	61.6
Grade 3	26	21.8
CTP CLASS		
A	24	20
B	60	50
C	36	30
Intrapulmonary Shuts (IPS)	43	35.8
Hepatopulmonary syndrome (Hypoxia + IPS)	10	8.3

In our study of 120 cirrhotic patients, hepatopulmonary syndrome was more prevalent in CTP class C (19.4%) while HPS was seen in 5% subjects in class B and none in class A.

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Correlation between HPS and child pugh score was statistically significant in our study with p-value 0.012 and chi square 8.87. In this study, in CTP –C out of 7 subjects, 6 subjects belong to moderate HPS and 1 patient belong to severe HPS, but in CTP- B , 1 patient belong to mild HPS and rest 2 had moderate HPS. Correlation between severity of HPS and child pugh score statistically not significant in our study with p-value 0.240. Correlation between subclinical HPS and child pugh score was statistically significant in our study with p-value 0.001 and chi square 13.77. (Table 4-7)

Table 4: DISTRIBUTION OF HPS IN CIRRHOTIC PATIENTS ON THE BASIS OF CTP CLASS.

CTP CLASS	HPS	
	YES	NO
A	0	24
B	3	57
C	7	29
Total	10	120

Table 5: CORRELATION OF HPS (HEPATOPULMONARY SYNDROME) WITH CHILD PUGH CLASS.

CTP CLASS	HPS		Total	p value (Chi square Test)
	YES	NO		
A	0	24	24	0.012
B	3	57	60	
C	7	29	36	
Total	10	110	120	

Table 6: CORRELATION OF HPS (HEPATOPULMONARY SYNDROME) SEVERITY WITH CHILD PUGH CLASS.

CTP CLASS	HPS SEVERITY			Total	p value (Chi square Test)
	MILD	MODERATE	SEVERE		
A	0	0	0	0	0.24
B	1	2	0	3	
C	0	6	1	7	
Total	1	8	1	10	

Table 7: CORRELATION OF SUBCLINICAL HPS WITH CHILD PUGH CLASS

CTP CLASS	SUBCLINICAL HPS		Total	p value (Chi square Test)
	YES	NO		
A	1	23	24	0.01

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B	15	45	60
C	17	19	36
Total	33	87	120

DISCUSSION

In the present study, among 120 patients, 51-60 years age group was most common, and 52 patients (43.5 %) were under this age group with mean age was 48 ± 10.6 years. Ansari et al [19] studied on the prevalence of hepatopulmonary syndrome in cirrhosis patients from southern part of India with results showing the most common age group was 31-40 years, mean age was 32 ± 8.6 years. Mona A et al [20] studied 50 cirrhotic patients showed most common age group 45-65 years (44 %) and mean age of 52.7 ± 8.2 years. Florence et al [21] showed cirrhosis in age group of 21-70 years among 120 patients with mean age of 51 ± 10.2 SD. Delayed presentation to healthcare facility is main reason for more of older age group patients in our study.

In our study, out of 120 patients, 103 patients (85.8%) were males and 17 patients (14.2%) were females and male to female ratio was 5:1,similar to Ansari et al [19] and Ali mokhtarifar et al [22].Since alcohol consumption is more in male population than female in northern part of India [23],cirrhosis due to alcohol consumption was found more common in males leading to more male patients in study population.

Among 120 patients, alcohol was the most common etiology in 72 patients (60%) followed by chronic hepatitis B infection in 9 (7.5%), chronic hepatitis C in 6 (5%) and other causes of cirrhosis in rest of 33 patients (27.5%). Similarly, De BK at al [24] showed most common etiology as alcoholic liver disease (70%) followed by chronic hepatitis B infection (15%), chronic hepatitis C infection (10%), autoimmune (1%) and cryptogenic (3%). Ansari et al [19] showed similar results with alcoholic liver disease as the most common cause in 24 patients (64%) out of 50 patients followed by chronic hepatitis B and chronic hepatitis C.

In our study the most common presenting complaint was abdominal distension in 83 patients (69.2 %) followed by swelling of legs in 74 patients (61.7 %),yellowish discoloration of eyes and skin in 63 patients (52.5 %) with most common respiratory complaints of breathlessness in 67 patients (55.8 %) and cough in 14 patients (11.6 %).Among HPS patients (n=10) , abdominal distension (90%) was the most common presenting complaint followed by breathlessness in 8 patients (80 %),yellowish discoloration of eyes and skin in 8 patients (80 %),swelling of legs in 7 patients (70 %).According to P Schenk et al [51] breathlessness was seen in 57 % among 34 HPS patients.

Ansari et al [19] study showed cough was most common presenting complain followed by breathlessness among 4 HPS patients. According to D Gupta et al [24], cyanosis (46%) and breathlessness (36%) were seen among 12 patients of HPS.

In our study, splenomegaly was seen in 96 patients (80 %) ascites in 90 patients (75%). clubbing in 17 patients (14.2%), cyanosis in 12 patients (10%) and spider naevi in 24 patients (20%). Splenomegaly was the significant as it indicates the presence of portal hypertension. Ansari et al [19] and D gupta et al [24] showed splenomegaly as the most common presenting finding followed by breathlessness. Ansari et al [19] showed splenomegaly in 38 patients out of 40 patients (95%) and D Gupta et al [24] showed splenomegaly in 50 patients (80 %).

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Out of 10 patients of HPS studied in our study, all had splenomegaly, clubbing and orthodeoxia while pallor, ascites and spider naevi were found in 9 patients (90 %), icterus in 8 patients (80 %) and cyanosis in 5 patients (50 %). Splenomegaly, pallor and clubbing were the significant finding in patients of cirrhosis with HPS seen in 100 % of patients.

P schenk et al [26] study showed clubbing and spider naevi in all patients of cirrhosis of liver with HPS. Abrams et al [18] showed significant correlation between cutaneous spider naevi and the severity of HPS. According to Ali Mokhtarifar et al [22] spider angioma, orthodeoxia, low serum albumin, and ascites were important clinical indicators for hepatopulmonary syndrome in cirrhotic patients. According to Robin ED et al [27] and Rodringuez roisin et al [28], clubbing and spider naevi are markers of intrapulmonary vasodilation.

In our study, 60 patients (50%) were in CTP class B, 36 patients (30%) were in CTP class C and 24 patients (20%) were in CTP class A.Majority of patients were in CTP class B. Child-Pugh classification is a good indicator of the severity of liver disease used for assigning the patients for liver transplantation.

In our study, out of 10 patient of HPS, 3 patients belong to Child Pugh class B and 7 patients belong to Child Pugh class C. In study of Abrams et al [18]showed significantly greater shunt fractions in Child-Pugh class B cirrhosis compared with Child-Pugh C class, Vachiery et al [29] showed that hypoxemic cirrhotic had a significantly higher Child Pugh score. Our study clearly showed a significant correlation between the HPS and Child-Pugh score.

In our study, grade 2 esophageal varices were the most common endoscopic findings. 20 patients (16. 6 %) patients showed grade 1 varices, 74 (61. 6 %) patients showed grade 2 varices and 26 patients (21. 8 %) showed grade 3 varices. In study by Ansari et al [19] showed grade 1 varices in 24 patients (60%) as most common endoscopic finding among cirrhotics.

In Stoller et al [30] study diagnosed HPS in 4 out of 98 cirrhotic patients. In the study of Aller and colleagues [31] a different formula for calculation of A-aO2 may have contributed to different results. Also use of different contrast agents may have contributed to the different results in some studies. Stoller et al [30] used indocyanine green dye solution which provides microbubbles with diameters of up to 90 µm, while our study and others (Hopkins et al, Abrams et al [18], Rolla et al [32,] and Aller et al [33]) used saline solution which creates microbubbles of 15–180 µm. Vedrinne et al [34] used a modified fluid gelatine solution which creates microbubbles of 10±2 µm. The frequency of intrapulmonary vasodilation and HPS was 38.8 % & 8.3 % respectively in our study.

In our study correlation between HPS and Child Pugh class was statistically significant (p-value of 0.012 & chi square of 8.87). In P Schenk et al [26] study of 98 patients showed statistically significant correlation between HPS and CTP class with (p value of 0.02). Study of 110 patients by Irfan et al [31] showed significant correlation between HPS and CTP class was statistically significant (p value of 0.01). Study of 17 patients by Vachiery et al [29] showed significant correlation between HPS and CTP class with a p value of 0.05.

In our study , out of 7 HPS patients in CTP class C ,6 patients belonged to moderate HPS and 1 patient belonged to severe HPS but among CTP class B patients , 1 patient belonged to mild HPS and rest 2 had moderate HPS. Correlation between severity of HPS and Child Pugh class was not found to be significant (p-value of 0.240). In contrast to study by Vachiery et al[29], correlation between severity of HPS and Child Pugh Score was statistically significant.

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Correlation between subclinical HPS and child Pugh class was statistically significant in our study with (p-value 0.01 & chi square 13.77). In literature no such study could be found which correlates “subclinical HPS” and CTP class.

Subclinical HPS was more common in CTP class B possibly because this class had more reserve of liver function than CTP class C. In “subclinical” HPS, patients had cirrhosis of liver and IPS (intra pulmonary shunts) positivity by contrast 2D echocardiography but no evidence of hypoxemia which signifies that inability to manage & treat cirrhosis of liver at early stages can lead to life threatening complication like HPS.

The present study had few limitations. The study population was small and it was an observational study without follow-up. The study population was from a limited region; hence it may not be representative of the general population. Study subjects were included from tertiary care centre so, they are more likely to have greater symptoms severity on presentation.

CONCLUSION

The development of pulmonary manifestations of cirrhosis has several clinical implications with regard to their management, as they carry poor prognosis. The diagnosis of HPS requires a high degree of suspicion among patients with cirrhosis. Since progression of CLD patient with HPS is very poor. All patients with cirrhosis should be screened for hypoxemia and screened for the presence of HPS.

All patients with HPS showed intrapulmonary shunting on contrast echocardiogram. Clinical signs of HPS like orthodeoxia and clubbing were observed in all patients with HPS. All HPS patients had esophageal varices indicating the presence of portal hypertension. There was a significant correlation between the HPS with Child-Pugh class and Subclinical HPS with Child-Pugh class. This correlation signifying that advanced CLD is more likely to have higher chances of developing HPS.

There is a need for further study in this area on larger patient group to evaluate the need of early testing to rule out “subclinical” HPS and HPS in early stages of cirrhosis to prevent mortality and morbidity in CLD patients.

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