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Prevalence of Pulmonary Artery Hypertension in Chronic Liver Disease: A Cross sectional Study

Dr Mahak Lamba[1], Dr Prem Kumar[2] Dr Praveen Raman Mishra[3], Dr Anshu Singh[4], Dr V.P.S. Punia[5], Dr Apoorv Singhal[6], Dr Akash Bharti[7]

[1]Assistant Professor, Department of Medicine, KGMU, Lucknow

[2]Assistant Professor, Department of Medicine, SMS&R, Sharda University, Greater Noida

[3]Senior Resident, Department of Medicine, AIIMS, Gorakhpur

[4]Assistant Professor, Department of Community Medicine, SMS&R, Sharda University, Greater Noida

[5]HOD, Department of Medicine, SMS&R, Sharda University, Greater Noida

[6]Senior Resident, Department of Medicine, SMS&R, Sharda University, Greater Noida

[7]PG Resident, Department of Medicine, SMS&R, Sharda University, Greater Noida

Corresponding Author: Dr Anshu Singh

Abstract:

Introduction: The chronic liver disease (CLD) patients usually develop portal hypertension over a period of time. CLD may be associated with pulmonary vascular abnormality in the form of pulmonary artery hypertension because of excessive vasoconstriction and vascular remodelling. Pulmonary vascular abnormalities leads to impaired arterial oxygenation thus have negative impact on survival of CLD patients. Chronic liver disease patients have some underlying subclinical cardiac abnormalities which are underdiagnosed such as diastolic dysfunction, systolic dysfunction, cardiomyopathy and pericardial effusion. Such subclinical cardiac abnormalities and pulmonary artery hypertension can be diagnosed at an early stage by echocardiography.

Material and Methods: The present study was carried out in Department of Medicine at a tertiary care hospital in North India on 50 patients with CLD fulfilling the inclusion criteria from July 2020 to June 2021.

Results: In our study the prevalence of pulmonary artery hypertension in CLD was found to be 56%. Among these patients who were having pulmonary artery hypertension 40% (20) belonged to mild category, 10% (5) moderate and remaining 6% (3) severe. Mild or moderate ascites was seen in 72% cases and upper gastrointestinal bleed in 56% of the cases. Pericardial effusion was found in 3% cases and diastolic dysfunction in 42% cases among the cases of PAH.

Conclusion: There was significant incidence of pulmonary arterial hypertension observed in chronic liver disease. The cardiac abnormalities when diagnosed at early stage will have prognostic impact in management of CLD.

Keywords: Chronic liver disease, Pulmonary artery hypertension, Echocardiography

Introduction: The liver detoxifies various metabolites, synthesizes proteins and produces biochemical that are necessary for digestion. Chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continues for at least 6 months. Several categories of chronic hepatitis have been recognized that includes chronic viral hepatitis, alcoholic, drug-induced and autoimmune chronic hepatitis. Chronic liver disease involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis in the liver. When fibrosis is so extensive that fibrous septa around parenchymal nodules alter the normal architecture of the liver lobule, the histologic lesion is defined as cirrhosis [1]. As the disease progresses, patients develop portal hypertension. In portal hypertension, constituents of venous blood arising from both the liver and portal system can directly injure the pulmonary vascular endothelium. The un-detoxified substances bypass the

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liver and affect the pulmonary vasculature and can result into Hepatopulmonary syndrome (HPS). The main pathogenetic mechanism in HPS is the dilatation of pulmonary vasculature, which leads to impaired gas exchange and progressive hypoxemia due to intrapulmonary shunting [2]. In contrast, obstruction to arterial flow in the pulmonary vasculature in the presence of increased pulmonary vascular resistance following excessive pulmonary vasoconstriction defines Porto-pulmonary hypertension (PoPH) and leads to an increase in right ventricle afterload and ultimately to right heart failure [3]. Both HPS and PoPH may present as dyspnea, though it is not rare for them to show no specific clinical symptoms [4]. Many patients with CLD may have some underlying subclinical cardiac abnormalities like cirrhotic cardiomyopathy, diastolic dysfunction, systolic dysfunction, pulmonary artery hypertension which remains undiagnosed [11,12]. For such undiagnosed subclinical patients, echocardiography acts as a sensitive tool to detect these cardiac abnormalities at an early stage[1]. Echocardiography plays a major role in unmasking various cardiovascular manifestations in patients with CLD. The most common Echocardiographic abnormality noticed are Left ventricular hypertrophy (LVH), Diastolic dysfunction, Systolic dysfunction, Pericardial effusion and Pulmonary artery hypertension [13]. Almost one-fourth of deaths in CLD are due to cardiac abnormalities, so early detection of sub clinical cardiac changes may be able to reduce morbidity and mortality [5,6,8]. Pulmonary arterial hypertension (PAH) is defined hemodynamically by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest. The WHO recognizes five groups of pulmonary hypertensions (PH) (1): (a) Idiopathic PAH, (b) PAH due to left heart disease, (c) PAH due to lung diseases and/or hypoxia, (d) Chronic thromboembolic PAH and (e) PAH with unclear multifactorial mechanisms.

Quantification of PAH

Mean Pulmonary Artery Hypertension	**Systolic PAP**	**Degree of PAH**
<25 mmHg	<40 mmHg	Normal
25-40 mmHg	40-60 mmHg	Mild
41-55 mmHg	60-90 mmHg	Moderate
>55 mmHg	>90 mmHg	Severe

Normal mPAP is defined as <20 mmHg, but PAH is defined as mPAP ≥25 mmHg [22].

PAH is a rare pathology with a poor prognosis and a median survival <3 years in the absence of treatment. Right heart catheterization is the gold standard for diagnosis [15, 18]. Echocardiographic assessment provides essential diagnostic and prognostic data to the clinician [7]. The demonstration of prognostic value of some echocardiographic parameters could diminish right cardiac catheterizations. Treatment is with vasodilator therapy to reduce PAP (pulmonary artery pressure) and PVR (pulmonary vascular resistance), and ultimately improve the right heart function. The proposed pathophysiology includes hyperdynamic pulmonary circulation leading to shear stress of pulmonary vasculature causing obstructive vasculopathy and increased pulmonary resistance. There is decreased Prostacyclins and increased Endothelin-1, Thromboxane-2, serotonin, interleukins and VIP (Vasoactive Intestinal Peptide) affect the pulmonary artery [9, 10].

So we planned this study to find out the prevalence of pulmonary artery hypertension in patients of chronic liver disease, with the help of echocardiography.

Aims & objectives

To determine the prevalence of pulmonary artery hypertension in patients of chronic liver disease, with the help of echocardiography.

To study the Correlation of PAH with severity and various metabolic parameters of CLD.

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Materials & Methods

Area of study: This was a cross-sectional observational study conducted in the in-patient department of General Medicine at a tertiary care hospital in North India on 50 patients with CLD fulfilling the inclusion criteria. A minimum 50 patients were recruited for the study purpose using non-random consecutive sampling from July 2020 to June 2021. A sample size of 50 was calculated with an expected frequency of cardiovascular complications to be 30 per cent. The confidence level was 80 per cent, and absolute precision was 5 per cent. Institutional Ethics Committee approval was obtained. A written informed consent was obtained from all the patients before collecting the data and tests from the study subjects. The inclusion Criteria includes-

CLINICAL CRITERIA- History of jaundice for more than six months and signs of chronic liver disease e.g. chronic liver disease stigmata, jaundice, ascites, hematemesis or melena, splenomegaly.

BIOCHEMICAL CRITERIA- Serum Total Bilirubin>1.5 mg/dL, SGOT>40 IU/L, SGPT>40 IU/L, Serum albumin<3 g/dL

RADIOLOGY CRITERIA- Ultrasound /CT scan showing shrunken or nodular liver with features of portal hypertension.

BIOPSY- If available showing cirrhosis.

Exclusion Criteria includes anyone of the following: Patients with primary cardiac or pulmonary disease, already diagnosed hypertensive patients, severe anaemia, diabetes mellitus, postpartum females and pregnant females.

Philips Affiniti 70c Ultrasound system machine was used for echocardiography in the echo Lab as per the standard protocols by experienced cardiologist and Size and structure of the heart, thickness of the wall of the cardiac chambers. Ejection fraction, Diastolic function, Cardiac output, any Heart muscle disease and cardiomyopathy were noted.

The history of patients was obtained by using semi structured pre-tested interview schedule. Clinical history, examination and laboratory details were recorded. Echocardiography was performed by a single specialist all throughout the study over the period of one year.

Data Analysis: Data obtained was analysed using standard Statistical Package for Social Sciences (SPSS) software. Descriptive results were expressed as Mean and percentages of various parameters in the different groups. Chi square tests using yates correction was used to assess the significance of difference in values of different parameters in between groups. P values <0.05 was considered significant and <0.01 was considered as highly significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) 21 trial version, International Business Machines Corporation (IBM, New York, USA).

Results: The total number of study subjects that is confirmed cases of chronic liver disease were 50, out of which the maximum number of study subjects were males that is 90% whereas females were found out to be only 10%. The maximum study subjects belonged to age group of 40-60 years that is 74% as represented in table number 1. Figure 2 represents the prevalence of pulmonary hypertension that was found out to be 56 % out of which 40% (20) belonged to mild category followed by moderate 10% (5) and severe 6% (3). Majority of the patient presented with the symptoms of chronic liver disease with confirmatory findings on ultrasound with mild or moderate ascites (72%) and upper gastrointestinal bleed in 56% of the cases. There was a significant association between PAH severity and Child Pugh Scoring as represented in table 3. Pericardial effusion was found to be in approximately 3% cases and diastolic dysfunction in around 42% cases among the cases of PAH.

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Table 1: Table representing age groups of the study subjects

Age Group	**Male** **Number (percentage)**	**Female** **Number (percentage)**	**Total** **Number (percentage)**
<=30	1(22.2)	0(0)	1(2)
30-40	4(88.9)	0(0)	4(8)
40-50	19(42.2)	1(20)	20(40)
50-60	15(33.3)	2(40)	17(34)
>=60	6(13.3)	2(40)	8(16)
Total	45(90)	5(10)	50(100)

Figure representing prevalence of pulmonary hypertension in the CLD patients

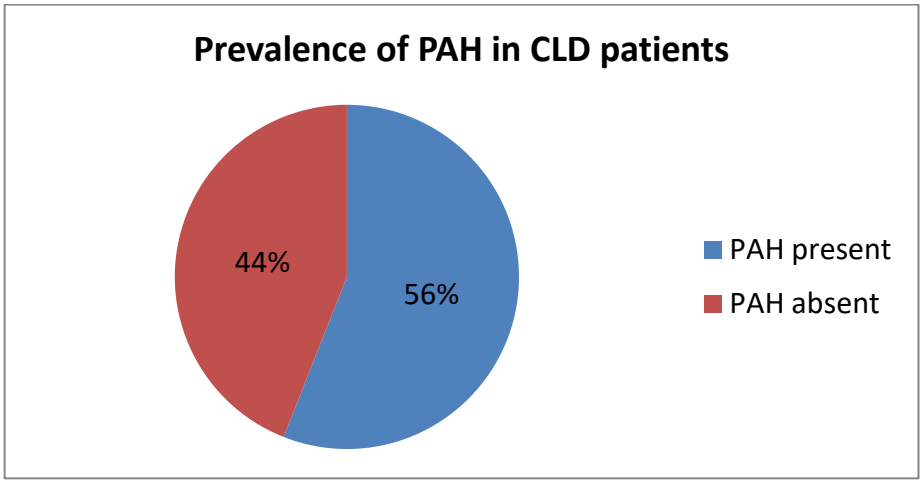

Table 2: Table representing association of Child Pugh scoring with pulmonary arterial hypertension

Child Pugh scoring		**PAH Severity**					Chi square Df P value
		Mild No. (%)	Moderate No. (%)	Severe No. (%)	No PAH No. (%)	Total No. (%)	
Class	a	0(0)	0(0)	0(0)	5(22.7)	5(10)	13.480 6 **0.036**
	b	06(30)	2(40)	01(33.3)	12(54.5)	21(42)	
	c	14(70)	3(60)	2(66.7)	5(22.7)	24(48)	
Total		**20(40)**	**5(10)**	**3(6)**	22(44)	50(100)	

*Chi square test is used after applying Yates correction.

Discussion: In the study, majority of patients that is 90% were males which was consistent with a study in India [14] and Denmark [13] that showed incidence of cirrhosis to be higher among men. On UGI endoscopy, 29 (69%) patients had oesophageal varices, but pulmonary hypertension was found only in 28 (56%) similar to the findings of a study in Texas [21], where portal hypertension was closely associated with development of PAH and unlike the findings of Khiangte [14] where HPS was present in only 40.6% patients. Platypnea and orthodeoxia were present more often in

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HPS patients in comparison to our study where dyspnea was the main complaint. Portopulmonary hypertension was seen in 8 (12.5%) subjects with no difference between HPS and non-HPS patients. Subjects with HPS had more severe liver disease. Maraghy ABS et al [16] reported the prevalence of HPS was 25.28% (22 out of 87 cases) and was higher than the prevalence of Portopulmonary hypertension, which was 5.7% (5 out of 87 cases). These findings does not match with studies done by Balde et al and Punekar et al [17, 19]. All these can be because of different study settings and places.

In our study fourteen of nineteen patients with CPS Grade C had mild PAH while 3 with CPS Grade C had moderate PAH. Pulmonary arterial hypertension was found to be more in Child class C as compare to Child class B and Child class A. This association between CPS and PAH was found to be significant along with having clinical correlation which was in contrast with other studies like Punekar [17] found Based on Child Turcotte Pugh score for severity of cirrhosis, 43% of cases were in Child class A, 45% in Class B and 12% in class C. The incidence of cardiac abnormalities increased with duration of chronic liver disease. In our study Pericardial effusion was found to be in only 3% cases and diastolic dysfunction in about 42% cases among the cases of PAH which is higher in comparison to study done by Punekar [17] where incidence of diastolic dysfunction was 32%, systolic dysfunction was 6%, pericardial effusion was 22% pulmonary arterial hypertension was 6% where as Balde [19] found that there was no significant association between echocardiographic changes and CPS in patients with liver cirrhosis. Though our findings were consistent with the study done by Ghayumi [20] where he noticed that left ventricular hypertrophy was present in 47.3%, diastolic dysfunction in 40%, pulmonary artery hypertension in 32.7%, and pericardial effusion in 3.6% of patients. This might be because of the less sample size that we have taken.

Conclusion: There was significant incidence of pulmonary arterial hypertension observed in chronic liver disease patients which increase with severity of illness. Incidence of subclinical cardiac abnormalities also increases with severity of chronic liver disease. Early detection of subclinical cardiac changes is important to reduce morality and mortality in chronic liver disease patients. These cardiac abnormalities when diagnosed at early stage will have prognostic impact in management of CLD.

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