Original Research Article

A Study of Pulmonary Hypertension in Patients with Cirrhosis of Liver and Portal Hypertension

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Abstract

Background and objectives: Portopulmonary hypertension is a well known complication of liver cirrhosis. This study aims to find the frequency of pulmonary hypertension in patients with cirrhosis of liver and portal hypertension and to determine the association between severity of cirrhosis using CHILD PUGH(CTP) classification and frequency of pulmonary hypertension (PAH).**Methods:** his cross sectional study was conducted on 151 patients with cirrhosis of liver and portal hypertension, diagnosed by ultrasonography and esophagogastroduodenoscopy. Echocardiography was done. A pulmonary arterial systolic pressure of more than 40mm Hg was taken as PAH. Data was analysed using SPSS version 21.0 by descriptive statistics and Chi Square test. **Results:** Of the 151 patients studied , most were 31-40 years(35.8 %), 88.7% were males. The maximum number belonged to CTP B. 6.6% of the study population had PAH, of which the majority belonged to CTP C. There was no statistical correlation between severity of cirrhosis and PAH (p-0.25).Female sex was associated with increased incidence of PAH and was statistically significant(p-0.00).**Conclusion:** Based on the findings of this study, there is a need for screening all patients with portal hypertension for PAH, As several studies have shown mortality benefit with early treatment and intervention for PAH.

Keywords: Portopulmonary hypertension; Esophageal varices; Cirrhosis.

Introduction

The term portal hypertension was coined by Gilbert in 1902. In 1937 ,Thompson verified the increase in portal pressure directly during laparotomy and portal hypertension was confirmed. It was followed in 1960 when Glisson at a dissection in London, established the portal vein as the vessel by which the blood was collected from the gastrointestinal tract and returned to the systemic circulation.

The global prevalence of liver cirrhosis ranges from 4.5% to 9.5% of the general population[1]. Early identification of its complications and their management is the mainstay of treatment for cirrhosis.

Portopulmonary hypertension(PoPH) is defined as development of pulmonary arterial hypertension(PAH) complicated by portal hypertension with or without advanced hepatic disease[2-5].

It has been hypothesised that pulmonary hypertension results from defective hepatic elimination of vasoconstrictive agents such as endothelin, produced in the splanchnic territory which reach the pulmonary arteries through porto-systemic shunts. A hyperdynamic circulatory state in cirrhosis patients also results in pulmonary artery shear forces, causing vascular remodelling, resulting in PAH[6].

A large autopsy series found the changes of pulmonary hypertension in 0.73% patients with cirrhosis, six times the prevalence in all autopsies[7]. Later, hemodynamic studies estimated the prevalence of this affliction between 2% and 5%. Another study showed that patients with PPH who did and did not take therapy, had a 5 year survival of 45% and 14% respectively. Patients who received liver transplantation with and without treatment for PAH had 5 year survival of 67% and 25% respectively, showing the importance of screening and treatment of PoPH[8]. Hence, this study is being taken up.

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Aims and Objectives

i.To study the frequency of pulmonary hypertension in patients of cirrhosis of liver with portal hypertension.

ii.To determine the association between severity of cirrhosis of liver using CHILD PUGH'S classification (ANNEXURE) and frequency of pulmonary hypertension

Methodlogy

Materials and Methods

Source of data

Patients of liver cirrhosis and portal hypertension attending to the General medicine outpatient department or admitted in wards of hospitals attached to Bangalore Medical College and Research Institute.

Method of collection of data(including sampling procedure if any)

A.Study design: Cross sectional study

B.Study period: November 2017- May 2019

C.Place of study: Hospitals attached to Bangalore Medical College & Research Institution, Bangalore

D: Sample size: 151

Based on the previous study conducted by Anikethana G.V, Ravikumar T.N, Chethan Kumar K[9], out of 100 patients with liver cirrhosis and portal hypertension, 17 had pulmonary hypertension. Hence p = 17.

The sample size calculation is as follows, using the formula: $N = Z^2_\alpha pq / d2$

Where Z_α is the standard table value at 95% CI,

$Z\alpha = 1.96$

p =17, q = 83, d = absolute precision = 6

N = (1.96)2*17*83/62
N =150.56
151 subjects with cirrhosis of liver and portal hypertension.

Annexure
Child Pugh's Scoring

Table 1: Child Pugh's Scoring

Factor	Units	1	2	3
S . Bilirubi N	mg/dl	<2	2-3	>3
S. Albumin	g/dl	>3.5	3-3.5	<3
Prothrombin Tim INR	Seconds prolonged	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Ascites		None	Easily Controlled	Poorly Controlled
Hepatic Encephalopathy		None	Minimal	Advanced

Child pugh a :5-6
Child pugh b : 7-9
Child pugh : > 9

Inclusion criteria

- 18 years and above of both sex
- Those willing to give informed consent
- Patients with cirrhosis of liver (Ultrasonogram(USG) showing altered echotexture and shrunken liver) and presence of portal hypertension (2 out of either Ascites with splenomegaly, Portal vein diameter more than 13 mm, portosystemic collateral venous communications on Ultrasonogram or oesophageal varices on Upper Gastrointestinal(GI) endoscopy.

Exclusion criteria

- Age < 18 years
- Adults with other clinical conditions which could lead to portal hypertension or pulmonary hypertension
- Patients not willing to give informed consent

G:Methodology for data collection

After obtaining clearance from institutional ethics committee, those patients willing to give informed consent and attending OPD or getting admitted to hospitals affiliated to Bangalore Medical College & Research Institute, during the period of November 2017 to May 2019 were taken up for the study.

Patients aged more than 18 years with cirrhosis of liver and portal hypertension were selected as per the ultrasonogram criteria showing altered echotexture, shrunken liver size and 2 out of either ascites with splenomegaly, portal vein diameter > 13mm, portosystemic collateral venous communications or oesophageal varices on oesophagogastroduodenoscopy. Demographic details were noted and detailed history was elicited with special reference to alcohol consumption, symptoms suggestive of portal hypertension and pulmonary hypertension. Detailed physical examination was carried out . Each subject underwent relevant investigations and the data was noted .

Child Pugh score was calculated for each patient. All the subjects were then

subjected to 2D Echocardiography (Pulmonary systolic artery pressure (PASP) > 40mm Hg at rest being taken as pulmonary hypertension)

Assessment Tools

- Proforma for written informed patient consent
- Study proforma
- USG Abdomen for cirrhosis of liver
- Oesophagogastroduodenoscopy for portal hypertension(varices)
- 2D Echocardiography(PASP > 40mm Hg)
- Relevant blood investigations
- Electrocardiogram
- Chest-X-ray

Statistical Analysis

Data was entered in Microsoft Excel and exported into SPSS version 21.0.

Data was analysed by descriptive statistics in the form of mean values, standard deviation and percentages. Chi Square test was used for association of qualitative variables. A p value<0.05 will be considered statistically significant.

Results

During the study period a total of 151 patients who fit into the inclusion criteria were studied. Of these , most were in the age group of 31-40 years(35.8 %)(Table 2). Most of the study population were males (88.7%) and the remaining 11.3% were women(17 out of 151) (Table 3). The Study population was categorised based on severity of cirrhosis using Child Pugh Classification.

Table 2: Distribution of The Patients Based on Age

Age (Years)	No. of patients (n)	Percentage (%)
< 30	10	6.6
31 – 40	54	35.8
41 – 50	46	30.5
51-60	26	17.2
61-70	12	7.9
>70	3	2.0
Total	151	100.0

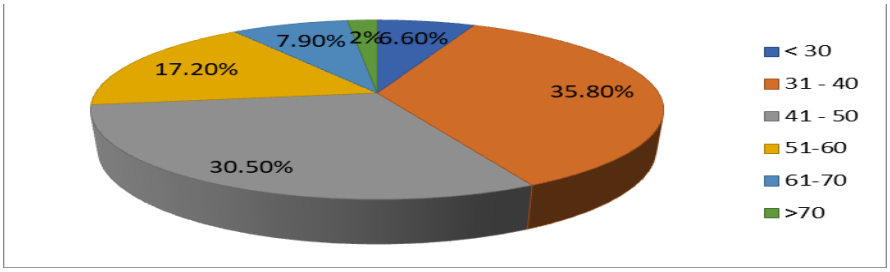

Fig 1: Graphical Representation of Age based distribution of patients

Table 3: Gender –Wise Distribution of The patients

Sex	(n)	Percentage(%)
Male	134	88.7
Female	17	11.3
Total	151	100.0

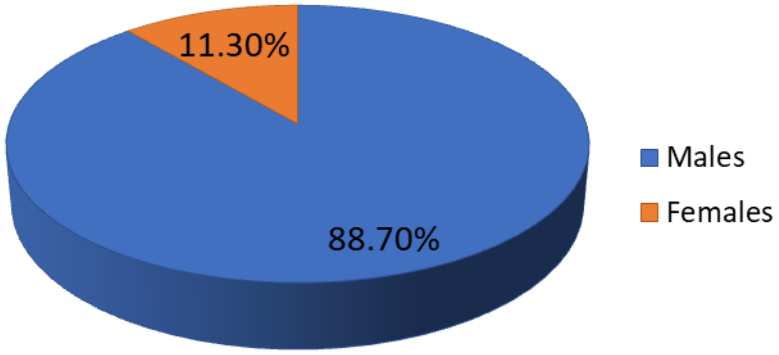

Fig 2: Graphical Representation of sex based distribution of patients

In each of the Severity category of cirrhosis, the mean age in Child Pugh Class A was **43.60+/-10.59**, in Class B was **45.21+/- 11.11** and in Class C was **44.67+/- 12.32**(Table 4),Out of the 151 patients, the maximum number belonged to Class B (Table 6). This included 77 patients (54.6%) of the total study population.In Class A, 25% were females and 75 % were males. Class B included 90.9% males and 9.1% females. Class C included 90.3% males and 9.7% females

Table 4: Mean Age Distribution of The Patients Based On Child Pugh Class

Child Pugh Class	(n)	Mean Age (years)	Std. Deviation of Age of patients
A	20	43.60	10.590
B	77	45.21	11.116
C	54	44.67	12.315

Outcome

When these patients who were diagnosed with Portal hypertension were subjected to 2D ECHO for identification of pulmonary hypertension, it was found that the mean PASP was 26.8+/- 5.6 in Class A, 25.57+/-6.22 in Class B and 29.85+/-8.70 in class C.(Table 4). A PASP of more than 40mm Hg was considered as pulmonary Hypertension. It was found in 6.6% of the total studypopulation, i.e 10 out of 151 patients with portal hypertension(Table 6) had pulmonary hypertension.

Table 5: Mean PASP Distribution of The Patients Based On CHILD PUGH Class

Child Pugh Class	(n)	Mean PASP (mm Hg)	Std. Deviation of PASP
A	20	26.80	5.644
B	77	25.57	6.227
C	54	29.85	8.701

The maximum number of patients with pulmonary hypertension was found in Child Pugh C (6 out of 10). However there was no statistical correlation between severity of Liver Disease and Pulmonary hypertension(p value- 0.25).

Table 6: Distribution of The Patients Based On Pulmonary Hypertension

Category	n	Percentage (%)
Patients without Pulmonary Hypertension(PASP<40mm Hg)	141	93.3
Patients with Pulmonary Hypertension(PASP>40mm Hg)	10	6.6
Total	151	100.0

Table 7: Child Pugh Class Wise Distribution of Patients With Pulmonary Hypertension

Pulmonary hypertension	Child Pugh Class			Total
	A	B	C	
No	19	74	48	141
Yes	1	3	6	10
Total	20	77	54	151
Chi-square value- 2.77				
P value- 0.25				

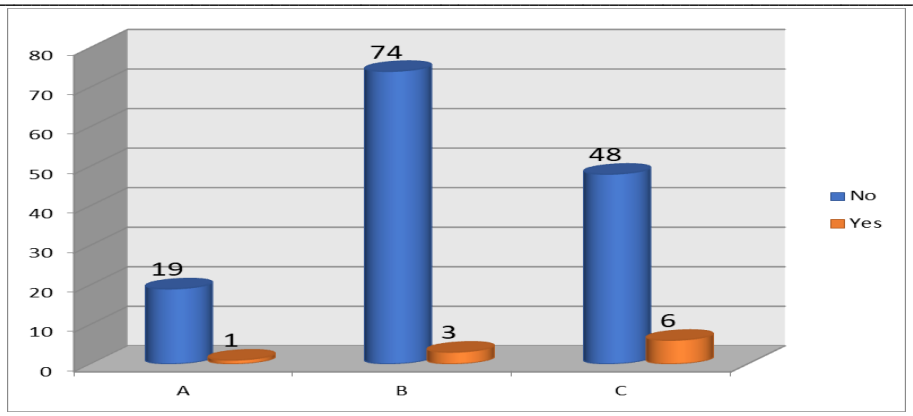

Fig 3: Graphical Representation of Classwise Distribution of patients with pulmonary Hypertension

Table 8: Cross-Tabulation of Gender And Pah

	PAH		Total
	Absent	Present	
Female	11	6	17
Male	130	4	134
Total	141	10	151
Chi-square value- 25.46			
P value-0.00*			

There was no significant correlation between age and development of pulmonary hypertension(p-0.415). However female gender was associated with increased incidence of pulmonary hypertension in patients with portal hypertension, which was found to be statistically significant(p-0.00)(Table 8)

Discussion

The prevalence of pulmonary hypertension in cirrhotic patients ranges from 2% to 20%, as reported by various studies carried out by right heart catheterisation[10,11].The wide variation stresses on the need for this study.

According to the study conducted by Gurghean and Tudor[12] 20% of the patients with portal hypertension developed pulmonary hypertension i.e 27 out of 116.

In a study by Auletta M et al[12] 83 patients with liver cirrhosis were assessed using 2D echocardiogram, out of which 20% had pulmonary hypertension.In our study however, out of 151 patients with Portal Hypertension, 10 had pulmonary hypertension (6.6%) Some other studies that were done using different methods of assessment are tabulated below.

Table 9:Study and related data

Study	Incidence of Poph	Method of Detection
Gurghean and Tudor[10]	20%	Echocardiography
Auletta et al[12]	20%	Echocardiography
Anikethana et al[9]	17%	Echocadiography
El Maraghy et al[13]	5.7%	Right heart Catheterisation
Colle et al1[4]	6.06%	Right Heart Catheterisation
Krowka MJ et al[15]	5.34%	Right heart Catheterisation
Hadenque et al[16]	2%	Right heart Catheterisation
Our study	6.6%	Echocardiography

The wide variation that was seen in the various studies was probably due to different cut-Offs of the PASP in the different studies. However our study shows values closest to those studies where pulmonary hypertension was assessed using Right Heart Catheterisation , which is considered the gold standard of Diagnosing Pulmonary Hypertension.

In our study, Out of the 10 patients with Pulmonary Hypertension, only 1 had history of dyspnea on exertion(10%). Hadengue et al[16] also found that 60% of patients with PAH did not show any symptoms. In their study, There was no significant association between age and development of PAH or Sexual preponderance and development of PAH. Anikethana et al[9] also did not find any significant correlation between progression of age and Development of Pulmonary Hypertension or association with sex.

However in our study, female sex had a significant correlation with development of pulmonary hypertension, although age did not have a significant association.

In our study, it was found that 5.26% of patients with Class A CTP, 3.89% of patients with Class B CTP and 11.1% of patients with Class C CTP had PAH. In our study, there has been no significant association between severity of liver disease and development of Portopulmonary Hypertension(p-0.25).

In the study by Gurghean and Tudor[10],among the patients with pulmonary hypertension, 30% were in Class A, 52% were in Class B, 19% were in Class C.The severity of the hepatic disease could be a determining factor, but in this study in which 64% of the patients were in Child-Pugh B and C classes the odds ratio for them to have pulmonary hypertension as compared to patients in class A was statistically not significant (p=0.36). Anikethana et al, Castro M et al, Ghayumi SM et al, Kawut SM et al, also found no association between severity of cirrhosis and PAH,hence consistent with ther findings. However, Auletta M et al,[12] found a higher prevalence of portal hypertension in more severe liver disease(as graded by Child Pugh classification.

Limitations of the study

- Small Sample size
- Right heart Catheterisation could not be done as the confirmatory test

Summary

This study was a cross sectional study done on patients with cirrhosis of liver and portal hypertension, to determine the association between pulmonary hypertension and portal hypertension, and to identify if a correlation exists between severity of cirrhosis of liver and pulmonary hypertension. It was done on 151 patients. It was found that the incidence of pulmonary hypertension in these patients was 6.6% (10out of 151). It was also found that female sex had a higher incidence of pulmonary hypertension(6 out of 17 patients), with statistically significant correlation. It was also found that the maximum number of patients with pulmonary hypertension belonged to CHILD PUGH Class C of severity, it was however not statistically significant. Hence, screening of patients with portal hypertension for pulmonary hypertension is necessary, as it detects asymptomatic pulmonary hypertension and facilitates its treatment.

Conclusion

This study explored the association between pulmonary arterial hypertension and cirrhosis of liver with portal hypertension. The incidence of pulmonary hypertension detected was 6.6% ,of whom 90% of the patients were asymptomatic. This indicates the need for screening of all patients with portal hypertension for pulmonary hypertension, as several studies have shown mortality benefit on early treatment and intervention for pulmonary hypertension.

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