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Study of portopulmonary hypertension in patients of cirrhosis of liver

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Abstract
Introduction: End stage liver disease and its complications are a leading cause of mortality among adults. One of the grave complications amongst numerous pulmonary afflictions in patients of end stage liver disease with portal hypertension is pulmonary hypertension. Its occurrence marks dismal prognosis. However, with better understanding of underlying pathogenetic mechanisms, early diagnosis can be achieved and which also helps in paving a way for novel therapeutics.
Aims: i) To evaluate the occurrence of pulmonary hypertension in patients of cirrhosis of liver with portal hypertension.
ii) To associate occurrence of pulmonary hypertension with severity of cirrhosis of liver.
Methods: A cross sectional study was conducted on eighty patients with liver cirrhosis without intrinsic cardiopulmonary disease. After a detailed history, all patients were subjected to thorough clinical examination, laboratory investigations, radiological investigations including abdominal ultrasound with portal vein Doppler study, chest X -ray, ECG and transthoracic 2D ECHO. The patients were also graded for severity of liver disease using Child Pugh Score.
Results: The study showed a male predominance with increased male to female ratio. And most of the patients belonged to lower socioeconomic strata. The occurrence of portopulmonary hypertension in cirrhotic patients was found in 12.5%. The presence of pulmonary hypertension was found to be increased in patients with advanced liver disease, severity as obtained by Child Pugh Score.
Conclusion: There is significant occurrence of portopulmonary hypertension in patients of liver cirrhosis and also that it is associated with the severity of liver disease in exponential manner. The early identification of pulmonary hypertension is crucial in view of prognosis and helps in guiding future management by speeding up orthotopic liver transplantation.

Keywords: portal hypertension, pulmonary hypertension, liver cirrhosis, echocardiography

1. Introduction

It is perfectly known that a liver plays a central role in maintaining health and homeostasis. Hence, a diseased liver heralds a multitude of complications in multiple organ systems. One of the vulnerable system is pulmonary system and one of the grave complications as a consequence of liver disease is pulmonary hypertension secondary to portal hypertension [1].

Pulmonary arterial hypertension (PAH) is defined as sustained elevation in resting mean pulmonary arterial pressure; mPAP >25mmHg at rest and > 30mmHg during exercise. However, portopulmonary hypertension (PPHTN) is a specific condition characterized by raised pulmonary artery pressure; mPAP > 25mmHg at rest and >30mmHg during exercise, elevated pulmonary vascular resistance; PVR >240dyne/sqcm and normal pulmonary capillary wedge pressure; PCWP <15mmHg with coexisting portal hypertension (portal pressure> 10mmHg). POPH is a subset of pulmonary arterial hypertension, accompanied by hepatic disease or portal hypertension in the absence of other known causes of pulmonary arterial hypertension. The reported prevalence of portopulmonary hypertension in cirrhotic patients ranges from 0.25 to 16%, which is influenced by patient characteristics, diagnostic criteria and the diversity of study designs [2].

Likely causative factors responsible for elevation of PAP in a patient of portal hypertension are [1]:

1. Hyperdynamic circulation and high cardiac output leading to increased shear stress on pulmonary circulation,
2. increased pulmonary intravascular volume,
3. Vasoconstrictive substances such as endothelins as well as pulmonary emboli.

Cirrhotic cardiomyopathy and intrahepatic AV fistulas are other liver related causes of hypertension [3]. It is found that prognosis of POPH is related to the severity of liver disease. However occurrence of POPH is not associated with the severity of liver disease.

Most common presenting symptom in patients with pulmonary hypertension is progressive dyspnoea on exertion; other less frequent include fatigue, palpitations, syncope, chest pain, hemoptysis and orthopnoea; with loud P2, systolic murmur and signs of right ventricular failure like elevated jugular venous pressure, ascites, pedal edema and occasionally anasarca on physical examination.

Portopulmonary hypertension once developed, the prognosis is dismal in absence of an intervention with a mean survival period of 15 months. Also, the absence of an animal model coupled with the rarity of disease has prevented a better

understanding of the pathogenetic mechanisms and thereby improved management of portopulmonary hypertension. Therefore, with scenario of paucity of researches and the rarity of disease in itself, in this study our aim is to evaluate occurrence of portopulmonary hypertension in cirrhotic patients and correlate with the severity of cirrhosis of liver shedding light on the pathobiology of the disease giving way to novel therapeutics and speeding up the way to orthotopic liver transplantation with diagnosis earliest possible [4].

2. Materials and methods

A cross sectional study was conducted in medicine department at Sir Sayajirao General Hospital, Vadodara during the period of November 2016 to November 2017. Total 80 patients with cirrhosis of liver were enrolled and studied.

Inclusion criteria

- Adult patients of either sex diagnosed as cirrhosis of liver due to any cause.

Exclusion criteria

- Patients with coexisting primary pulmonary pathology.
- Coexisting intrinsic heart disease.
- Chronic heavy smokers.

All enrolled patients were subjected to detailed history and clinical examination. The diagnosis of liver cirrhosis with portal hypertension was made on the basis of history, clinical examination, laboratory investigation and ultrasound examination including Doppler study to assess portal vein diameter. The severity of liver cirrhosis was assessed according to the Child Pugh classification. Patients of liver cirrhosis with portal hypertension were assessed for pulmonary hypertension by clinical history and examination followed by electrocardiogram, chest x ray and trans thoracic 2D echocardiography.

All patients were subjected to following

- Complete clinical examination following detailed history with special emphasis on per abdominal and cardiovascular system examination.
- Laboratory investigations including complete blood count, random blood sugar, renal function tests with electrolytes, liver function tests including bilirubin (total, direct and indirect), SGPT, SGOT, PT INR and serum total protein and albumin, HBsAg, HCV and HIV.
- Abdominal ultrasound to assess liver echotexture, portal vein diameter, splenomegaly and ascites.
- Chest X Ray (PA) view to look for cardiomegaly and pulmonary artery.
- Electrocardiogram to look for changes of right ventricular involvement ascertaining pulmonary hypertension.
- Two Dimensional trans thoracic echocardiograph. Pulmonary hypertension was diagnosed using following parameters: right ventricular systolic pressure (RVSP), tricuspid regurgitation and right ventricular hypertrophy.

Statistical analysis was not done since Chi square test was not applicable.

3. Results

The results of the study are summarised as follows:

The total number of patients in the study was 80. Male to female ratio was 15:1 with significant male preponderance. Most patients were from lower socioeconomic strata.

The mean age of patients was 42 ± 10 years.

Table 1: Sex distribution of study population.

Sex	No. of patients	Percentage
Male	75	93.75
Female	5	6.25
Total	80	100

On history, common presenting symptoms were abdominal distension (80%), jaundice (77.5%), pedal edema (68.5%), hematemesis (68.5%), dyspnea on exertion (58.75%), fatigue (61.25%) followed by less frequent symptoms melena (28.75%), bleeding PR (5%), abdominal pain (15%), cough (7.5%) and chest pain (1.25%). Symptoms like palpitation and syncope were not present. (Figure1)

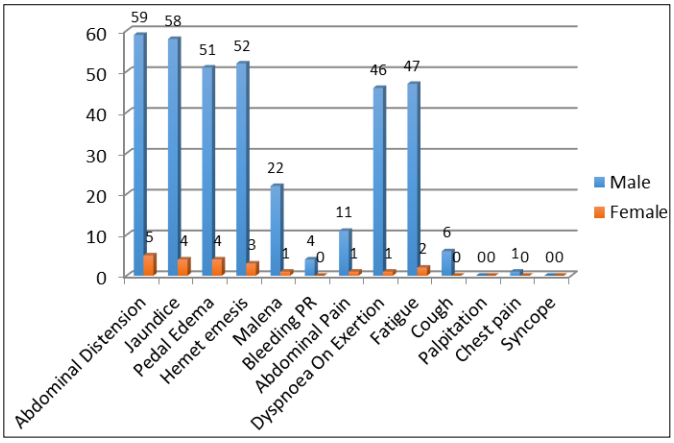

Fig 1: Symptomatology profile in study population

On examination, pallor was found in 72.5% patients, icterus in 82.5%, pedal edema in 67.5%, clubbing in 37.5% and koilonychia in 41.25%. Cyanosis was found in none and lymphadenopathy was noted in 2 patients. (Figure 2)

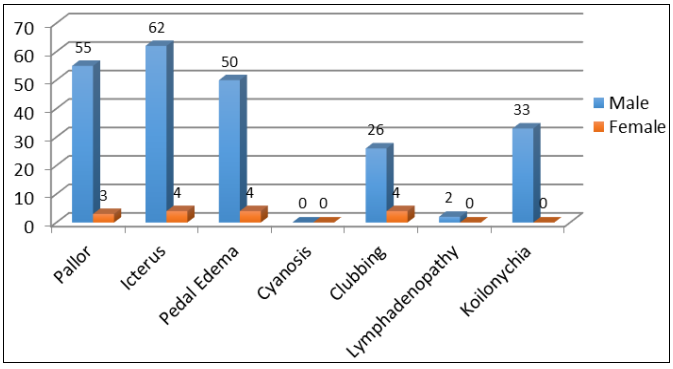

Fig 2: Clinical features in study population

On per abdominal examination, splenomegaly was found in total of 48 patients out of 80 amounting to 60%. Total 64

patients (80%) had signs s/o free fluid in abdomen. Dilated veins were documented in 23 patients (28.75%) and hemorrhoids in 12 patients (15%).

On CVS system examination, RV apex was found in 5 patients of total 80, impaired left 2nd ICS was found in 6 patients amounting to 7.5% with loud P2. S2 split was found in 3 patients (3.75%) and systolic murmur in total of 10 patients.

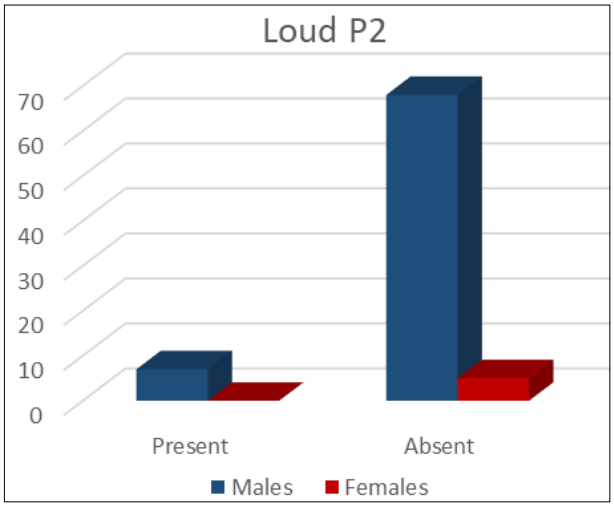

Fig 3: Presence of RV apex in study population

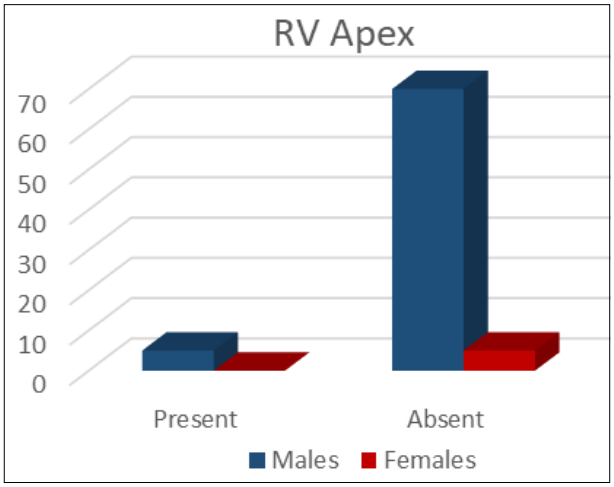

Fig 4: Presence of loud P2 in study population

Portal Vein Diameter

Table 2: Analysis of PV diameter on ultrasound abdomen

Portal Vein Diameter(mm)	Male	Female	Total Patients	Percentage
≤ 11	15	0	15	18.75
>_11	55	5	65	81.25

Portal hypertension as analysed by ultrasound using portal vein Doppler was noted in 65 patients (81.25%) (Table 2). On further investigations, 6 of these were found to have changes of right ventricular enlargement on ECG. However, on transthoracic 2D echo, RVH was noted in 8 patients and that right ventricular systolic pressure (RVSP) as an indirect marker of pulmonary hypertension was found to be elevated in 10 patients (Table 3, Figure 5).

RVSP (Right Ventricular Systolic Pressure)

Table 3: Analysis of RVSP in study population

RVSP (mmHg)	Male	Female	Total Patients	Percentage
<_18	65	5	70	87.5
>18 - 40	8	0	8	10
41 - 60	2	0	2	2.5
>60	0	0	0	0

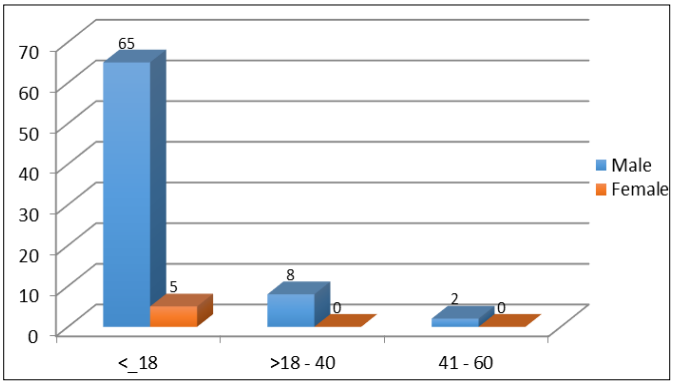

Fig 5: Analysis of RVSP in study population

Portopulmonary hypertension was found in 10 patients, out of which one was of Child Pugh Class B and rest 9 were of class C.

Patients with Pulmonary Hypertension

Table 4: Distribution according to Child Pugh Score in patients with pulmonary hypertension

Child PUGH Score	Male	Female	Total Patients	Percentage
A	0	0	0	0
B	1	0	1	10
C	9	0	9	90

Table 5: Correlation between PV diameter and RVSP, indicating correlation between portal and pulmonary hypertension

	PV Diameter		Total patients
	<11 mm	>_11 mm	
RVSP			
<_18 mmHg	15	55	70
> 18 mmHg	0	10	10
Total patients	15	65	80

Above table (Table 5) shows that of the total 80 patients, PV diameter ≥ 11mm was noted in 65 patients suggesting portal hypertension. Of these 65 patients, RVSP > 18mm Hg was found in 10 patients indicating pulmonary hypertension (15.3%). Of the total 80 patients, pulmonary hypertension was noted in 12.5% of patients. This is consistent with other studies [15]. This also shows that 2D ECHO is sensitive, non-invasive, cheap and easily available investigation to diagnose early onset of portopulmonary hypertension in resource constrained settings, in view that the most symptom on development of pulmonary hypertension being dyspnoea on

exertion which is non-specific and has multifactorial causes in liver cirrhosis.

4. Discussion

4.1 General aspects

The present study showed skewed distribution of study population which is representative of the population of cirrhotic patients seen in clinical practice; as described by Sherlock, the male preponderance can possibly be attributed to increased frequency of alcoholism in males [5].

Most patients were from lower socio-economic strata. All the studies reviewed showed cirrhosis of liver to be the most common in lower socio-economic class, probably due to high prevalence of alcoholism and poor nutrition in this group.

Alcoholism was noted in 88% of patients with daily intake of more than 50grams for more than five years, mostly country liquor and was more prevalent in males [6, 7].

The present study showed abdominal distension as most common symptom followed by jaundice and pedal edema, followed by hematemesis and melena, dyspnoea on exertion and fatigue. Dyspnoea on exertion, being the common symptom of pulmonary hypertension followed by fatigue was found in many and was also attributed to confounding factors like anemia. Other symptoms like cough and chest pain were found in 6 and 1 patients respectively.

4.2 On General Examination:

In the present study, pallor was noted in 72% of patients with koilonychia in 40% of them; this being attributed to multiple causes of anemia in patients with cirrhosis i.e. nutritional, upper and lower g.i bleeding, gut edema, anorexia and alcohol induced in alcoholics. Icterus was noted in 82% and pedal edema in 64%. The other features of liver cell failure like clubbing was found in 37.5% and lymphadenopathy in 2.5% patients, consistent with other studies.

4.3 On systemic examination

On examination in the present study, spleen was found to be enlarged in 60% of patients. Hepatomegaly was found in 27.5 % of patients. Ascites was found in 80% of patients. Dilated veins and haemorrhoids were found in 28.75% and 15% patients respectively.

Further, on cardiovascular system examination, RV apex was found in 6.25% of patients. Impaired left 2nd intercostal space was found in 7.5% with loud P2. S2 split was found in 3.75% with systolic murmur present in 12.55% of patients. However, murmur had a confounding factor- anemia in our study. Patients with severe anemia are prone to have murmurs.

4.4 Investigations

On investigation on hemogram, significant patients were found to be anemic, about 84%. The mechanisms are multifactorial as enlisted above. Total count less than 4000 as expected was present in only 10%, the only probable explanation being exclusion of patients with other comorbidities and complications.

Thrombocytopenia is a common finding in cirrhosis as reported by Sherlock and is consistent with our present study. Liver plays an important role in synthesis of clotting factors which results in prolongation of prothrombin time which corroborates with our study.

The liver enzymes and serum bilirubin were only slightly raised in majority of patients in this study. Sherlock *et al.* [5] had similar results in their study.

Hypoalbuminemia is frequently encountered in patients of liver cirrhosis, factors causing being:

1. Defective synthesis by damaged liver.
2. Hypervolemia
3. Loss in ascitic fluid.

Chiltsle and Munshi demonstrated hypoalbuminemia in 80% cases of liver cirrhosis which corroborates with the finding of present study.

In the present study, globulins are increased in majority of patients with reversal of A: G ratio in 88.75% of cases as is commonly observed in most studies.

Splenomegaly, splenic diameter >120mm was noted in 78.75% of patients in present study which is consistent with study of E. Giannini *et al*., Filippo Schepis *et al*. [8, 9].

Portal vein diameter greater than 11 was noted in 81.25% of patients [16, 17]. It has been noted in various studies that portal vein diameter varies with age and sex and has a wide range ranging from 7- 15 mmHg In one such it was found that the mean portal vein diameter was 9.60 ± 1.42mm for both sexes and that it has a positive correlation with body mass index [10, 11, 12].

Ascites is noted in 87.5% of patients in present study. All the above features are consistent with portal hypertension.

Further the patients were graded according to severity as per Child Pugh's score. Of the total 80 patients in the present study, Class A housed 8 patients (10%), Class B 17 patients (21.25%) with maximum number of patients in Class C, 55 patients (68.75%). As compared to previous studies, in our present study, there are more patients in Class B and C, this probably is due small sample size and delayed treatment seeking behaviour in general due to lack of awareness.

In above patients, cardiomegaly on chest X-ray was noted in 5 patients. Changes of right ventricular enlargement was found in 6 patients in ECG [13]. On trans thoracic 2D echo, RV hypertrophy was noted in 8 patients. In most cases RVSP, right ventricular systolic pressure equals the pulmonary artery pressure. A normal mean pulmonary artery pressure is 12 – 16 mmHg. Mild pulmonary hypertension is in range of 25 – 40, moderate in range of 41 – 60 and severe is more than 60 mmHg. Also, that the RVSP gives a peak value and not mean pressure i.e. rather than an average [14]. In the present study, RVSP more than 18mmHg on 2D echo was noted in 10 patients (12.5%) suggesting pulmonary hypertension, out of which 8 patients were having mild pulmonary hypertension (RVSP 18 – 40 mmHg) and 2 having moderate pulmonary hypertension(RVSP 40 – 60 mmHg). This is in concordance with most studies who showed prevalence ranging from 0.25% to 16% as shown by F.S. Benjaminov *et al*. [2] and Marius *et al*. [15]. The most common presenting symptom in patients with POPH is progressive dyspnoea on exertion which is found in 7 patients (8.75%) out of total 10 (12.5%) patients. Other symptoms such as fatigue, palpitation, chest pain or syncope are less frequent which corroborates with our

study. Benjamin and Douglas [13] showed that physical findings indicating pulmonary hypertension are generally subtle and may be completely absent, most common ones being loud P2 and a systolic murmur present in 7 and 2 patients respectively in our study.

However, the present study showed the association of portopulmonary hypertension with the severity of liver cirrhosis as graded by Child Pugh Score to be significant with 85% patients of portopulmonary hypertension in Class C. This is not in concordance with the studies conducted previously probably because of small sample size.

5. Conclusion

Liver cirrhosis is associated with unique pulmonary complications, one of which is portopulmonary hypertension. Also, its association with severity of liver is found to be significant. Therefore, early identification of pulmonary hypertension is of utmost importance since it affects the prognosis and guides the future management by speeding up orthotopic liver transplantation. Transthoracic Doppler echocardiography is sensitive, non-invasive, cost effective and easily accessible investigation for the early detection of portopulmonary hypertension as well as for exclusion of intrinsic heart disease causing pulmonary hypertension in resource constrained settings.

Conflict of Interest: None

6. Acknowledgment

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