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PORTO PULMONARY HYPERTENSION AND CIRRHOSIS OF LIVER: AN ASSESSMENT OF ITS FREQUENCY AND ASSOCIATED RISK FACTORS

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Contribution
MU conceived the idea and designed the study. Data collection and manuscript writing was done by MU, MZQ, AT, IHN, BM, and KM. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Objectives: To determine the frequency and factors leading to of portopulmonary hypertension among cirrhosis of liver patients

Methodology: One hundred and eleven (111) patients previously diagnosed with cirrhosis of liver due to any cause were included in the study from 15th June 2016 till 14th July 2017. All of the patients had echocardiography done. Portopulmonary Hypertension (PoPH) was diagnosed by Echocardiographic signs as per recommendation of European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Tricuspid Regurgitation Velocity of >3.4 m/s Or Tricuspid Regurgitation Velocity of >2.9 m/s but <3.4m/s along with one of the following signs :Right ventricle / left ventricle basal diameter ratio >1, Pulmonary artery diameter > 25 mm, early diastolic pulmonary regurgitation velocity >2.2, m/s Inferior cava diameter >21mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration), Flattening of the interventricular septum.

Results: Out of 111 patients, 70 (63%) were male and 41(37%) were female. The mean age of the patients was 51±8.7 years. The cause of cirrhosis noted in the documents at the time of diagnosis was chronic hepatitis C in 62/111 patients (55.85%), chronic hepatitis B in 34/111 (30.63%), alcoholic cirrhosis in 4/111 (3.6%), autoimmune hepatitis in 3/111 (2.7%) and cryptogenic cirrhosis in 1/111(1%). After echocardiography 08 (4 males and 4 females) out of 111 patients (7.2%) were diagnosed as having Portopulomonary Hypertension (PoPH) and low hemoglobin level was linked autonomously with hazard of PoPH

Conclusion: Viral related cirrhosis is the most common cause of cirrhosis in this part of the world. Echocardiographically confirmed Portopulomonary Hypertension (PoPH) is well reported cardiopulmonary complication of cirrhosis of liver. Among various risk factors for PoPH low haemoglobin (anaemia) was found to be a significant risk factor. Portopulmonary Hypertension (PoPH) is a very important contributing factor in morbidity and mortality in patients of cirrhosis which needs to be identified and confirmed before referring any patient of cirrhosis for Liver Transplant

Keywords: portopulmonary hypertension (PoPH), cirrhosis of liver

INTRODUCTION

Advancing hepatic fibrosis, consequent to various etiologies eventually result in liver cirrhosis, which is featured by altered parenchymal architecture as well as impaired liver functions. These patients are likely to developa multitude of complications, resulting in decreased life expectancy.[1,2] Two major pulmonary complications of cirrhosis include Hepatopulmonary Syndrome (HPS) and Portopulmonary Hypertension (PoPH).[3,4] Portopulmonary hypertension (PoPH) is contemplated to be there when pulmonary arterial hypertension (PAH) is present in a patient having portal hypertension in the absence of any other cause of the PAH such as cardiac disorders(congenital), drugs and connective tissue disease,)[5-7]

The prevalence of portopulmonary hypertension (POPH) is varied among the different patient population studied. The incidence rates of POPH in patients having portal hypertension, range from 2 to 9%.[8] while Savale L et al.[9] reported the estimated prevalence up to 5% among patients with portal hypertension with or without cirrhosis. But Chen HS et al.[10] have reported slight higher prevalence i.e. 10% in their study of 100 patients with cirrhosis.

The prognosis is worse for patients with portopulmonary hypertension because of associated liver disease, where a median survival was observed to be 6 months and a 5 years' survival rate to be just around < 10%[11] although recent studies have found a 5-years survival of 50%.[12] The reported estimate is of a 35%[13] mortality in patients having had Liver Transplant with a mean pulmonary artery pressure (mPAP) >35 mmHg. Such patients could be refused a transplant prospect unless the mPAP is brought quite under 35 mmHg through medicines. Recently Li J et al.[14] reported 14 patients out of 223 (6.3%) with 57% (8 out of 14) mortality before Liver Transplant could be done.

Cardiac catheterization of right heart is the benchmark to diagnose and to find exact degree of pulmonary hypertension. But it is recommended to perform the procedure in centers with expertise as it is a difficult procedure and associated with serious complications. So for screening patients for PoPH in patients with advance cirrhosis,

Transthoracic echocardiography (TTE) is the method recommended[15] and reliable enough to estimate cardiac function and hemodynamics.[16] Multiple sings of echocardiography are laid down by ESC (European Society of Cardiology) and ERS (European Respiratory Society) for diagnosis of PAH has also recommended multiple echocardiographic signs to diagnose Pulmonary Hypertension.[17]

In Pakistan, Hussain R et al.[18] and Shafiq M et al.[19], have worked on Pulmonary artery hypertension and Hepatopulmonary Syndrome respectively and not on portopulmonary hypertension. The rational of my study was to elucidate the current magnitude of cirrhotic patients with portopulmonary hypertension by using the diagnostic criteria recommended by ESC/ERS and to identify factors leading to it among liver cirrhotic patients thereby by recommendation could be made for regular screening of such patients could be made. Thereby early treatment could be initiated before their definitive treatment (liver transplant) is planned. Therefore, objective of this study was to determine the frequency and factors leading to portopulmonary hypertension in patients having cirrhosis of liver.

METHODOLOGY

This cross sectional study was conducted for one year from 15th June 2016 till 14th July 2017 at Memon Medical Complex Karachi, Pakistan, a secondary care Hospital with fully equipped clinical laboratory and echocardiography unit. The approval from the hospital committee and informed consent for inclusion in study was obtained after informing all the patients and explaining the study protocol in detail. Consecutive patients of liver cirrhosis irrespective of etiology of Child Class B and C, both males and females over 18 years to 60 years of age and patients who had not under gone echocardiography within one month for any reason were included in the study. Patients with known cardiovascular diseases, patients with history of smoking, lung diseases and Inferior cava hypoxia, connective tissue disorder or venous thromboembolism / pulmonary embolism were excluded.

Cirrhosis was confirmed on clinical (stigmata of chronic liver disease), radiological (ultrasonologically), and biochemical parameters used for chronicity of liver. Histopathological basis was also applied to diagnose Cirrhosis wherever required. Investigations were sent to assess the gravity of liver disease as per Child Pugh Score[20] or MELD score.[21] These included complete blood count, prothrombin time with INR, liver function tests, renal functions and ultrasonography.

All patients underwent Echocardiography on Toshiba-Aplio MCM 1754TS- Japan by a consultant cardiologist with more than 10 years of experience to diagnose pulmonary hypertension. The images performed were 2Dechocardiograms (two-dimensional), M-mode echos and tissue Doppler imaging after which portopulmonary hypertension was confirmed as per guidelines/ diagnostic criteria laid down by ESC/ERS that is patients with Tricuspid Regurgitation Velocity of >3.4 m/s or, Tricuspid Regurgitation Velocity of >2.9 m/s but <3.4m/s along with

either one of these signs: Right ventricle to left ventricle basal diameter ratio >1, early diastolic pulmonary regurgitation velocity >2.2 m/s, pulmonary artery diameter > 25 mm, Interventricular septum flattening, a diameter >21mm of Inferior vena cava along with reduced inspiratory collapse (<50% on a sniff or <20% on quiet inspiration) were considered as having portopulmonary hypertension.

The data was analyzed by employing IBM SPSS version 20. The statistics of descriptive format included mean ± standard deviation (SD) or median (range) of continuous data while the categorical data was computed for frequencies and percentages. Comparisons with the groups of patients having or not having PoPH were elucidated Mann–Whitney U-tests and via t-tests. Listing as well as data grade was compared by using Fisher's exact test, chi-square test and rank sum test. Variables which showed statistical significance that is ($p < 0.2$) were made part of the logistic regression among patients with or without PoPH.

RESULTS

The Demographic Profile of the patients is presented in Table 1. Out of 111 patients, 70 (63%) were male and 41(37%) were female. The mean age of the patients was 51±8.7 years. The cause of cirrhosis noted in the documents at the time of diagnosis was chronic hepatitis C in 62/111 patients (55.85%), chronic hepatitis B in 34/111 (30.63%), alcoholic cirrhosis in 4/111 (3.6%), autoimmune hepatitis in 3/111 (2.7%), cryptogenic cirrhosis in 1/111(1%) while the remaining 7/111 patients (6.3%) did not have any cause mentioned or identified in their record. 23 out of 111 patients(20%) were having hepatocellular carcinoma on Triphasic CT scans done previously.

Table 1: Demographic Profile of the patients

Characteristics	Descriptive Summary
Total number of the patients	111
Male	70(63%)
Female	41(37%)
Mean age of the patients	51±8.7 years
Cause of Cirrhosis	
Chronic Hepatitis C	62 (55.85%)
Chronic Hepatitis B	34(30.63%)
Alcoholic	4(3.6%)
Autoimmune Hepatitis	3(2.7%)
Cryptogenic	1(1%)
No cause identified	7(6.3%)
Hepatocellular Carcinoma	23 (20%)
Hemoglobin	9.4 ± 2.5 mg/dl
Creatinine	0.7 ± 0.4 mg/dl
Bilirubin	4.5 ± 2.4 mg/dl
Albumin	3.0 ± 0.7 mg/dl
Child- Pugh Score	8 ± 2 (range:6-12)
MELD	16 ± 4 (range: 06-36).
Portopulomonary Hypertension (PoPH)	
Not Present	103(92.8%)
Present	08(7.2%)
Male	04(3.6%)
Female	04(3.6%)
MELD	17 ± 3 (range: 06-36).

The mean values recorded were as Hemoglobin: 9.4 ± 2.5 mg/dl, Creatinine: 0.7 ± 0.4 mg/dl, Bilirubin: 4.5 ± 2.4 mg/dl, Albumin: 3.0 ± 0.7 mg/dl. As all the patients were either Child's Class B or C, the mean Child- Pugh Score was 8 ± 2. (range was 6-12). Likewise the mean MELD score was 16 ± 4 (range from 06-36). After echocardiography 08 (7.2%) (4 males and 4 females) out of 111 patients were diagnosed as having Portopulomonary Hypertension (PoPH). In patients with Portopulmonary Hypertension (PoPH), the means values for same variables were lower than the overall study population (Table 2)

Table 2: Profile of patients with Portopulomonary Hypertension

Profile of patients with Portopulomonary Hypertension (PoPH) (n=08/111	
Hemoglobin	8.4 ± 2.9 mg/dl
Creatinine	1.1 ± 0.4 mg/dl
Bilirubin	6.5 ± 3.2 mg/dl
Albumin	2.80 ± 0.7 mg/dl
Child- Pugh Score	9 ± 2(range:7-12)
MELD	17 ± 3 (range: 06-36).

Echocardiographic Profile with patients with PoPH:

The Echocardiographic profile is presented in Table 3. The Mean Pulmonary artery diameter was 26.3±3.5 mm (27.0,26.0,24,27.5,27.5,26.4,26.0,26) while the mean Tricuspid regurgitation velocity (TRV) was 3.1± 0.5 m/s (min 2.9 m/s and max 3.4m/s). Right ventricle / left ventricle basal diameter ratio >1 or Flattening of the interventricular septum was found in 4 out total 8 patients while Pulmonary regurgitation velocity > 2.2 m/s was noted in all of the 8 patients. There was no substantial alteration in thecardiac function, and cardiac chamber size in the patients with or without PoPH.On multivariate logistic regression analysis, we found that only low hemoglobin level had independent association with risk of PoPH though we also assessed, MELD score, Child Pugh Score and albumin. (Table 4)

DISCUSSION

Portopulmonary Hypertension (PoPH) accounts for up to 10% of Pulmonary Artery Hypertension groups.[12] PASP was previously used to detect Pulmonary artery Hypertension but underestimation and overestimation in PASP and cannot be reliably used.[17,22] Nowadays, the most recommended method is echocardiography (TTE)[15] which is reliable enough to estimate cardiac function and hemodynamics.[16] European Society of Cardiology (ESC) and the European

Table 3: Echocardiographic Profile of Patients with Portopulmonary Hypertension

Case Number	Gender	Tricuspid regurgitation velocity (TRV) m/s	Right ventricle / left ventricle basal diameter ratio >1 or Flattening of the interventricular septum	Pulmonary regurgitation velocity > 2.2 m/s	Pulmonary Artery Diameter mm
1	Male	3.4	No	Yes	27.0
2	Female	2.9	No	Yes	26.0
3	Female	3.1	Yes	Yes	24.0
4	Female	3.0	Yes	Yes	27.5
5	Male	2.9	No	Yes	27.5
6	Male	3.0	Yes	Yes	26.4
7	Female	3.2	Yes	Yes	26.0
8	Male	3.1	No	Yes	26.0

Table 4: Multivariate Logistic Regression analysis

Variable	p-value	Odds Ratio (OR)	95% CI
MELD	0.6	1.04	0.88–1.204
Child Pugh Score	0.41	1.32	0.680–2.554
Hemoglobin	0.005	0.95	0.93–0.988
Albumin	0.62	0.96	0.867–1.114

Respiratory Society (ERS) for diagnosis of PAH has also recommended the above mentioned multiple echocardiographic signs to diagnose Pulmonary Hypertension which we have used for this study and found the prevalence quite the same as of previous studies.[8-10,14]

Our study also have the similar finding as were in Chen et al.10 and Li J et al.[14] that low levels of Hemoglobin is a risk factor which is quite independent for PoPH. The patients who develop PoPH needs to be treated in order to improve survival and quality of life until they are provided the definitive treatment in the form of Liver Transplant otherwise unless PAH-specific therapy is offered, patients having PoPH will have a persistent poor prognosis even after LT.[14], [23-24]

Regarding the limitations of our study, as mentioned previously the gold standard for diagnosing PAH and PoPH is the Right Heart Catheterization in the setting of liver disease, however none of our patient was diagnosed by RHC and we used an alternative echocardiography signs. It is essential that patient diagnosed having PoPH should be confirmed by RHC in specialized centers.

CONCLUSION

Portopulmonary Hypertension (PoPH) is a very important contributing factor in morbidity and mortality in patients of cirrhosis which needs to be identified and confirmed before referring any patient of cirrhosis for Liver Transplant.

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