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Original Article

Echocardiography as a Screening Modality for Portopulmonary Hypertension in Patients with Cirrhosis and Chronic Viral Hepatitis

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ABSTRACT

Objective: To assess porto pulmonary hypertension by echocardiography in patients with cirrhosis and chronic viral hepatitis.
Study Design: Comparative cross-sectional study.
Place and Duration of Study: Gastroenterology and Cardiology Departments Combined Military Hospital, Multan Pakistan, from Mar to Dec 2020.
Methodology: Fifty patients with cirrhosis due to chronic hepatitis C, B/D, with Child-Turcotte-Pugh score>6, Model for End Stage Liver Disease–Sodium score>9, were compared to a Control-Group of 50 patients with chronic liver disease due to chronic hepatitis C, B/D; for the frequency of portopulmonary hypertension in the former group. In addition to pulmonary artery pressures, tricuspid regurgitation, right ventricle to left ventricle base ratio, and right ventricle tricuspid annular plane systolic excursion were also assessed.
Results: Four patients (8%) with cirrhosis (irrespective of severity) had porto pulmonay hypertension, and none in the Control-Group. The median pulmonary artery pressure in the Patient-Group was 20 mmHg (15-46), and in the Control-Group was 17 mm Hg (15-20). The Child Turcotte Pugh, Model for End Stage Liver Disease–Sodium parameters, pulmonary artery pressure and tricuspid annular plane systolic excursion were deranged in the Patient-Group and showed statistical significance. The area under the ROC curve for pulmonary artery pressure in the Patient-Group was 0.803.
Conclusion: In patients with cirrhosis, 8% had portopulmonary hypertension. Echocardiography is an important screening method for the assessment of portopulmonary hypertension in this patient population.

Keywords: Chronic viral hepatitis, Cirrhosis, echocardiography, Porto pulmonary hypertension, Right ventricle tricuspid annular plane systolic excursion.

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INTRODUCTION

Portopulmonary hypertension [PPHT] is the development of Pulmonary Artery Hypertension [PAH] in portal hypertension.[1,2] PPHT can develop in patients with various aetiologies of portal hypertension, however patients with cirrhosis account for most of the patients.[3] For diagnosing PPHT, other causes of PAH, such as chronic left heart failure, chronic hypoxic lung disease, and chronic thromboembolism, should be ruled out, amongst others.[4]

Like Pulmonary Hypertension (PH), PPHT is taken as mean pulmonary artery pressure, mPAP>25 mmHg at rest, and the presence of portal hypertension as evidenced by an elevation of hepatic venous pressure gradient, HVPG>5 mmHg, or suggested clinically by the presence of splenomegaly, signs of portosystemic shunts, thrombocytopenia, or oesophagal varices/abdominal varices.[1,5] The severity of PPHT is based on European Respiratory Society ERS criteria, graded as mild (25≤mPAP<35 mm Hg), moderate (35≤mPAP<45 mm Hg), and severe (mPAP≥45 mm Hg).[6] PPHT accounts for between 4-10% of patients with cirrhosis.[1,7,8]

Transthoracic echocardiography is a readily available noninvasive tool to assess PPHT in patients with cirrhosis and chronic liver disease with portal hypertension. As such, it has been endorsed by the world professional societies.[9,10] The present study was thus undertaken to assess the frequency of portopulmonary hypertension and related echocardiographic parameters in our patients with cirrhosis and chronic viral hepatitis.

METHODOLOGY

The comparative cross-sectional study was conducted at Combined Military Hospital, Multan Pakistan, from March to December 2020. The Hospital Ethical Review Committee approved the study (CMH Multan file no. 10/Trg). With an overall prevalence of 1% pulmonary hypertension in patients with cirrhosis

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in general, the sample size calculated via online sample size calculator (ClinCalc).

Inclusion Criteria: Patients of either gender, with cirrhosis from chronic HCV, HBV/HDV, with Child-Turcotte-Pugh (CTP) score of more than>6, and Model for End Stage Liver Disease–Sodium (MELD-Na) score>9were assessed for portopulmonary hypertension, were included in the study. The Control-Group consisted of patients suffering from chronic HCV, HBV/HDV with CTP score<6 and MELD score<9.

Exclusion Criteria: Patients less than 18 and more than 80 years of age, with a history of congenital heart disease, an alternative aetiology of Pulmonary Hypertension (PH), active treatment with pulmonary vasodilator drugs, or those with incomplete data were excluded from the study.

After informed consent, the patients were listed via consecutive sampling. Patients had physical examinations conducted during clinic visits. There was no history of shortness of breath. Physical exam included stigmata of chronic liver disease, hepatomegaly and special emphasis on signs of portal hypertension: grades of encephalopathy, splenomegaly, ascites, and superficial abdominal veins. Heart examination focused on loud P2 and systolic murmur along the left sternal edge and chest auscultation.

Investigations carried out were blood CP, bilirubin, alanine aminotransferase, alkaline phosphatase, albumin, prothrombin time, INR, activated partial thromboplastin time, urea, creatinine, sodium, potassium, ECG, chest X-ray (PA) view, ultrasound abdomen and upper GI endoscopy (where indicated) for endoscopic signs of portal hypertension; varices and portal hypertensive gastropathy in patients with cirrhosis.

Child-Turcotte-Pugh (CTP),[11] and Model for End Stage Liver Disease–Sodium,[12] MELD-Na scores were used to delineate cirrhosis. CTP score incorporating bilirubin, albumin, PT/INR, ascites and encephalopathy, with a score of>6 for patients with cirrhosis. The new Organ Procurement and Transplantation Network (OPTN) Model for End Stage Liver Disease formula,[13] was used to calculate the MELD-Na score by online calculator, with cirrhosis patients scoring>9. MELD-Na was used instead of MELD,[12] because low serum sodium is associated with disease severity, indicates free water retention, is an indirect marker of portal hypertension and is associated with increased mortality.

Two classified cardiologists performed echocardiographic examinations using commercially available ultrasound systems (Vivid E9 with XDclear, General Electric, USA). Images were obtained in the left lateral decubitus for parasternal and apical views and in the supine position for subxyphoidal views using 1.5-4.0MHz transducers. The examination included 2D echocardiography for anatomical imaging and Doppler echocardiography to evaluate velocities. The Doppler measurements were carried out over three cardiac cycles during expiration. Right ventricular systolic pressure was calculated using the modified Bernoulli's equation.[14] As no patient in either group had right ventricular outflow obstruction or pulmonary stenosis, the systolic pulmonary artery pressure was considered equal to right ventricular systolic pressure. Other parameters considered were Tricuspid Regurgitation as mild, moderate, and severe, right ventricle to left ventricle basal diameter ratio >or<1, and Tricuspid Annular Plane Systolic Excursion (TAPSE).

M-mode echocardiography in the apical four-chamber view was used to measure TAPSE. In this mode, an image demonstrated the systolic longitudinal displacement of the lateral tricuspid annulus toward the apex, the distance between end-diastole to end-systole. As the septal attachment of the tricuspid annulus was relatively fixed, the main component of longitudinal systolic motion occurs at the former; the more displacement, the better the RV systolic function. A value of <17 mm was considered abnormal. TAPSE decreases with worsening Pulmonary Arterial Hypertension and can broadly predict prognosis.[15]

Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. The quantitative variables were presented as median (interquartile-range). The categorical variables were presented as frequencies and percentages. The data had a non-normal distributed; the two groups were compared by non-parametric tests: Wilcoxon's rank sum test for continuous variables and the chi-square test for categorical variables. The *p*-value of <0.05 was considered statistically significant.

RESULTS

One hundred patients were included in the study and divided into two groups. Out of 50 patients in Patient-Group, 4(8%) had elevated pulmonary artery pressures of more than 25 mmHg. The median (IQR) age in the study population was 55(19) years, while in

the Control-Group was 39(17) years. The median (IQR) CTP score was 7(2), and MELD-Na was 15.5(8) in the Patient-Group. Similarly, all variables of CTP and MELD-Na (bilirubin, albumin, prothrombin time, INR, creatinine, sodium, ascites and encephalopathy) were more adverse in the Patient-Group as compared to the Control-Group and showed statistical significance. (Table-I). Of 4 patients, one had moderate, and three had mild portopulmonary hypertension. By CTP and MELD-Na criteria, the underlying liver disease ranged from mild to severe, thus underscoring that the severity of liver dysfunction does not influence the development of PPHT. The right ventricular TAPSE was less than 17 mm in all patients with PPHT. The

Table-I: Characteristics of Patients with Cirrhosis and Chronic Viral Hepatitis (n=100)

Characteristics	Group-1 with CirrhosisChild-Turcotte-Pugh Score (CTP)>6, Model for End Stage Liver Disease Sodium score (MELD-Na) > 9	Group-2 Chronic Viral Hepatitis (Control) CTP<6, MELD–Na <9	*p*-value
Age, years	55 (33-79)	39(17-78)	< 0.001
Gender			
Male Female	29(58%) 21(42%)	26(52%) 24(48%)	0.546
Aetiology			
Hepatitis C Virus Hepatitis B Virus Hepatitis D Virus	41(82%) 10(20%) 2(4%)	43(86%) 9(14%)	
Child-Turcotte-Pugh Score			
(CTP)	7(5-12)	5N.B. The Child-Turcotte-Pugh Score is constant (i.e. 5) in Group: CTP<6,MELD–Na <9.	< 0.001
Model for End Stage Liver Disease–Sodium score			
(MELD-Na)	15.5(9-32)	7(7-8)	< 0.001
Bilirubin, µmol/L	28.5(6-150)	11(6-20)	< 0.001
Albumin g/L	29.5(18-39)	39.50(31-49)	< 0.001
Prothrombin time, secs	19(14-30)	15(14-18)	< 0.001
International Normalised			
Ratio	1.4(1.1-2.2)	1.1 (1.1-1.2)	< 0.001
Creatinine, µmol/L	94.50(55-228)	82.21(56-98)	< 0.001
Sodium, mmol/L	135(123-142)	140(135-140)	< 0.001
Ascites No ascites Mild Moderate Large	21(42%) 20(40%) 7(14%) 2(4%)	50(100%)	< 0.001
Encephalopathy No Encephalopathy Mild Moderate Severe	19(38%) 19(38%) 10(20%) 2(4%)	50(100%)	< 0.001
Right Ventricle- Tricuspid Annular Plane Systolic Excursion, mm			
(RV-TAPSE)	20.5(12-23)	24(21-25)	< 0.001
Mean Pulmonary Artery Pressure, mm Hg	20(15-46)	17(15-20)	< 0.001

Table-II: Echocardiographic Parameters of Patients with Portopulmonary Hypertension (n=4)

Age(yrs)	Child-Turcotte-Pugh Score (CTP) Score)	Model for End Stage Liver Disease Sodium (MELD-Na Score)	Pulmonary Artery Pressure (mmHg)	Tricuspid Regurgitation	Right Ventricle-Tricuspid Annular Plane Systolic Excursion (RV–TAPSE) mm	Right Ventricle /Left Ventricle Ratio (RV/LV Ratio)	Ejection Fraction (percenta) (EF) (%)
55	6	9	46	Moderate	12	<1	50
48	10	13	41	Mild	16	<1	60
70	8	19	29	Mild	14	<1	60
56	11	20	36	Mild	15	<1	55

RV/LV ratio was normal in all four patients, and no patient had preload dysfunction, as was indicated by the near-normal ejection fraction in all 4 patients (Table-II). Figure shows the area under the ROC (Receiver Operating Characteristic) curve for pulmonary artery pressure in the Patient-Group, 0.803, (p<0.001,95% Confidence Interval, CI,0.717-0.890).

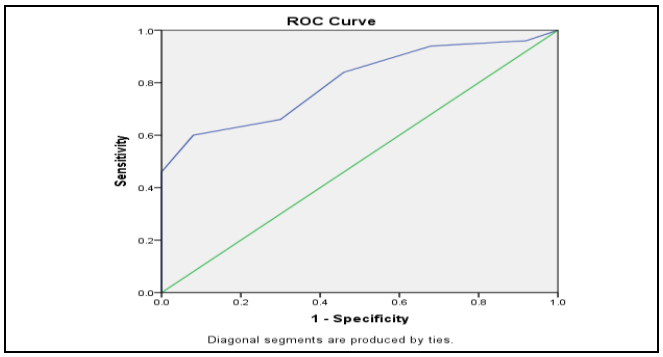

Figure: Receiver operating Characteristic (ROC) Curve for Portopulmonary Hypertension in the Patient-Group

DISCUSSION

Portopulmonary Hypertension is a serious complication of portal hypertension that affects the functional status, management, liver transplant assessment, and prognosis (survival) of patients with cirrhosis.[14] The risk of development of PPHT is independent of the severity of liver function, but survival depends on the degree of liver dysfunction. One study on a cohort of 637 patients, reported that survival was dependent on the severity of cirrhosis and better in liver transplant patients vis a vis non-transplant patients.[15] Krowka *et al.*, in 2006 in a prospective study of consecutive 1235 liver transplant patients screened over a 10-year period, who also had right heart catheterization, documented PPHT in 5.3% of patients.[7] Another study reported the prevalence of PPHT in 6% of patients.[16] Generally, PPHT accounts for 4-10% of patients with cirrhosis.[17] In the present study, the frequency of portopulmonary hypertension in patients with cirrhosis in our population group was 8%, which is in keeping with the abovementioned studies.

Portopulmonary hypertension has a similar histologic picture to Pulmonary Arterial Hypertension, characterized by media hypertrophy, endothelial and smooth muscle proliferation, remodelling of pulmonary artery lamina muscularis, vasoconstriction and thrombosis. The increased pulmonary vascular resistance thus causes raised pulmonary arterial pressure, which leads to right heart failure and a fatal outcome if left untreated.[18] The echocardiographic characteristics useful in determining pulmonary hypertension are an amalgamation of peak tricuspid regurgitant velocity, right ventricular size, right ventricular/left ventricular basal diameter, interventricular septal function, inferior vena cava diameter fluctuation with respiration, early diastolic pulmonary regurgitant velocity, end-systolic right atrial area, pattern of systolic flow velocity, and diameter of pulmonary artery.[19]

With the advancement of equipment and refinement of echocardiographic techniques, there has been incorporation of a combination of new parameters such as tricuspid annular plane excursion (TAPSE), grades of tricuspid regurgitation, dilated inferior vena cava, and pulmonary vascular resistance.[20,21] The RV-TAPSE in our patients with PPHT was less than 17mm.

LIMITATIONS OF STUDY

Ours was a comparative cross-sectional study with a matched patient and a Control-Group; it had a few limitations also. The number of cohorts was small. Some advanced echocardiographic techniques, such as pulmonary artery diameter, estimated pulmonary vascular resistance assessment, and right heart catheterization, could not be carried out due to echocardiographic equipment and coronary angiography logistic-related factors, respectively.

CONCLUSION

The frequency of portopulmonary hypertension in our patients with cirrhosis was 8%, irrespective of the severity of the cirrhosis. Echocardiography plays an important role in screening and evaluating patients for portopulmonary hypertension.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SA: & IAK: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

WURK: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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