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Prevalence of Portopulmonary Hypertension in Patients with Chronic Liver Disease; A Cross-Sectional Comparative Study

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Objective: To determine the prevalence of PoPH in patients with chronic liver disease

Methods: Adult patients ⩾18 years) diagnosed of CLD at the University of Calabar Teaching Hospital, Nigeria were recruited over a 10 month period from June 2018- April, 2019. The cases were age and sex matched with controls that had no symptoms or signs of CLD. All patients had trans-thoracic echocardiography (TTE). All parameters for the diagnosis of pulmonary arterial hypertension (PAH) were assessed based on recommendations of the American/ European Echocardiographic Association.

Keywords: *Porto-pulmonary hypertension, chronic liver disease, Trans-thoracic Echocardiography.*

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Prevalence of Portopulmonary Hypertension in Patients with Chronic Liver Disease; A Cross-Sectional Comparative Study

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Abstract- Background: Portopulmonary hypertension (PoPH) is an uncommon complication of chronic liver disease (CLD) defined by mean pulmonary artery pressure (mPAP)≥ 25mmHg at rest, pulmonary vascular resistance (PVR)>240 dyne/sec/cm^{-5} in the presence of portal hypertension (PoH). Literature on its prevalence amongst CLD patients in Nigeria is scanty.

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Methods: Adult patients (≥18 years) diagnosed of CLD at the University of Calabar Teaching Hospital, Nigeria were recruited over a 10 month period from June 2018- April, 2019. The cases were age and sex matched with controls that had no symptoms or signs of CLD. All patients had trans-thoracic echocardiography (TTE). All parameters for the diagnosis of pulmonary arterial hypertension (PAH) were assessed based on recommendations of the American/ European Echocardiographic Association.

Results: A total of 160 individuals participated in the study (80 cases of CLD and 80 healthy controls). The M: F ratio was 2.8:1. Hepatitis B virus infection was the aetiologic agent of CLD in 73.75% of cases. The mPAP was significantly higher in CLD patients (21.3 ± 10.1mm Hg versus 14.1 ± 7.6mm Hg; p <0.001) although only 5% had estimated mPAP>25mm Hg and 1.25% had PoPH. Thus, the prevalence of PoPH in this study was 1.25%. The estimated PVR and the systolic function of the right ventricle was not significantly different between the cases and the controls (p>0.05).

Conclusion: The prevalence of PoPH is low in our CLD cohort and most of these patients were females with HBV-related CLD.

Keywords: Porto-pulmonary hypertension, chronic liver disease, Trans-thoracic Echocardiography.

I. Introduction

Portopulmonary hypertension (PoPH) refers to the development of pulmonary arterial hypertension (PAH) in the setting of portal hypertension (PoH). This can result in significant right ventricular dysfunction, right heart failure and ultimately death. It is increasingly being recognized in chronic liver disease (CLD) patients because of its associated adverse outcome.[1,2] A study in Romania demonstrated that the prevalence of PoPH in cirrhotic patients was 3.7%.[3] The prevalence of PoPH amongst liver cirrhotic patients in Nigeria has not been formally documented. PoPH is defined by mean pulmonary artery pressure (mPAP)≥ 25mmHg at rest as confirmed by right heart catheterizations, pulmonary vascular resistance (PVR) >240dyne/sec/cm^{-5}, in the presence of PoH.[4,5] However, during the 6th world symposium on pulmonary hypertension (WSPH) in 2018, the value of mPAP was changed to ≥20mmHg.[6] However, mPAP≥ 25mmHg was used for this study. Pulmonary capillary wedge pressure (PCWP) < 15mmHg was previously part of the diagnostic criteria forPoPH but many of these patients may have volume overload and coexisting left ventricular dysfunction associated with cirrhotic cardio myopathy (CCM) which can cause the PCWP to exceed 15mmHg and so, it is no longer included in the diagnostic criteria.[4]

The pathophysio logical mechanism underlying the development of PoPH has not been fully elucidated. It was postulated that PoPH develops because of the increased sheer stress within the pulmonary vascular bed as a result of the hyper-dynamic circulation in CLD patients. In addition, there is increased level of vasoconstrictors such as endothelin-1, angiotensin II and thromboxane B_2 either produced locally within the pulmonary vascular bed or shunted into the pulmonary circulation from the hepatic bed. These substances leads to pulmonary endothelial damage, vascular remodeling and micro thrombosis.[7] PoPH causes increase in right ventricular (RV) afterload leading to RV ischemia, dilatation, and failure.[8] The clinical symptoms of PoPH are non-specific and may include dyspnea, fatigue, chest pain and some patients may not manifest any symptoms.[8]

Transthoracic echocardiography (TTE) is a recommended method to screen for PoPH in CLD.[9,10] Right cardiac catheterization is necessary to confirm the diagnosis but it is invasive and not usually available. Moreover, the procedure requires highly skilled personnel to distinguish PoPH from other cardiovascular derangements associated with CLD.

The impact of PoPH on morbidity and mortality of patients with CLD is independent of the severity of the PoH; while mild PoPH does not significantly influence outcome, moderate to severe PoPH can affect survival in CLD and is considered an absolute contraindication

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to liver transplantation because of increased risk of perioperative mortality.[11] In a study of survival in PoPH, Swanson et al[12] reported that patients who had PoPH and received no treatment for it had a five-year survival of 14% while those who received therapy but no liver transplant had a five-year survival of 45% and amongst patients who had liver transplant, five-year survival for those who received therapy for PoPH was 67% compared to 25% in those who did not receive treatment.

CLD remains one of the leading causes of in-hospital mortality in Nigeria; ranking fifth behind infections, chronic kidney disease, stroke and heart failure.[13,14] However, not much is known about the prevalence of PoPH in these patients.

II. Objective

To determine the prevalence of portopulmonary hypertension in patients with chronic liver disease.

III. Methodology

a) Study Design/Setting

This was a cross-sectional comparative study conducted at the Medical Outpatient Department and Medical wards of the University of Calabar Teaching Hospital, Calabar, Cross River State, Nigeria over a 10 month period from June 2018- April 2019.

b) Study Population

Adult patients aged≥ 18 years presenting with features of CLD were consecutively recruited into the study. Subjects with hypertension, diabetes mellitus, retroviral disease and other causes of PoPH such as underlying cardiovascular disease, chronic obstructive pulmonary disease) were excluded from the study. Controls were recruited from members of staff and patient relatives with no evidence of CLD and no underlying risk factor for pulmonary hypertension. The cases were age and sex matched with controls

c) Data Collection

Eighty consecutive adults with diagnosis of CLD (chronic hepatitis, liver cirrhosis and primary liver cell carcinoma) seen at the Gastroenterology unit of UCTH were prospectively recruited from the MOPD and medical wards of UCTH. All patients gave a written informed consent and were assessed with a structured questionnaire (developed for the purpose of this study by the authors) to obtain socio-demographic data (age, gender, alcohol consumption and smoking), symptoms and signs of liver decompensation, symptoms and signs of cardiovascular dysfunction and medication history. The patients were asked to stop medications that might interfere with the study protocol like β-blockers for at least 48 hours before the study. Biophysical, biochemical measurement as well as resting transthoracic echocardiography was done.

d) Diagnostic Criteria for CLD

CLD was diagnosed based on a combination of clinical features such as presence of peripheral stigmata of CLD (palmer erythema, finger clubbing, leuconychia, spider naevi, gynaecomastia in males), jaundice, hepatomegaly, splenomegaly and ascites. Biochemical parameters (deranged liver enzymes, thrombo-cytopenia, hypoalbuminemia and coagulopathy), hepatitis B and C serology, radiological and liver histology if there was no contraindication to liver biopsy. Severity of CLD was assessed using model for end-stage liver disease (MELD) score and categorized into 3 classes; class 1= ≤ 9, class 2 = 10-20, class 3 = > 20.

e) Diagnostic criteria for PoPH using Trans- thoracic Echocardiography

All patients had trans- thoracic echocardiography (TTE). Standard images were obtained through the apical four chamber, parasternal long axis and parasternal short axis views. All parameters were assessed based on recommendations of the American/ European Echocardiographic Association.[15]Right ventricular systolic function was assessed by determination of the tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) was assessed using tricuspid regurgitation velocity (TRV) and right atrial pressure (RAP)

$$\text{Pulmonary artery systolic pressure} = 4TRV^2 + RAP.$$

Mean PAP was obtained using pulsed wave-doppler study of flow across the pulmonary valve during systole in the parasternal short axis view to determine the right ventricular acceleration time (RV ACT). Mean PAP was calculated using the formula; 79 – (0.45 x RV ACT).

Pulmonary vascular resistance (PVR) was estimated using the TRV and the timed velocity integral of the right ventricular outflow tract (TVI_{RVOT}) in the equation shown below-

$$PVR = TRV/TVI_{RVOT} \times 10 + 0.16.$$

Right ventricular systolic dysfunction was considered present if TAPSE was < 17mm while the normal cut off for TRV was 2.8m/s. The upper limit of PASP was 40mmHg and mPAP was 25mmHg. Increased PVR was considered present when it was greater than 3 Wood units (240dynes.cm/s^2). RV basal dimension was estimated at end-diastole using a RV focused apical 4-chamber view. The RV basal dimension was defined as the maximal short axis dimension in the basal one third of the RV seen on apical 4 chamber view. RV basal dimension greater than 4.2cm was considered abnormal.

f) Sample Size Determination

This was calculated using Cochran's formula[16]n= Z^2Pq/e^2 wheren is the desired sample

population, Z is the desired confidence interval set at 95%. P is the proportion of patients with PAH in CLD which was 3.7%. [3] d is the desired precision of 5%.The minimum sample size of 54.7 was rounded up 80 after accounting for 10% attrition rate.Eighty patients with CLD and equivalent number of age and sex matched controls were recruited.

g) Statistical Analysis

All data collected were analyzed using the IBM SPSS version 20.0 (SPSS, Inc. Chicago, Illinois, USA). Continuous variables were described using mean and standard deviation while categorical variables were presented as percentages. Chi-square test was used for comparisons between categorical variables while Fishers exact test was used where > 20% of the expected frequencies was <5.The independent sample T-test was used for comparisons between continuous variables. Statistical significance was set at p-value less than 0.05.

IV. Results

a) Demographic Characteristics of Study Population

A total of 160 individuals participated in the study out of which 80 were those with CLD, the remaining 80 were healthy controls. Males were 118 (73.8%) while females were 42 (26.2%) of the population giving a male to female ratio of 2.8:1. The mean age of patients with CLD was similar to the controls (42.0±12.6 years versus 40.8±9.9 years; p = 0.208). Other socio-demographic characteristics are shown in Table 1.

Table 1: Comparison of Socio-Demographic Characteristics of Cases and Controls (N=160)

Variable		Arm of Study: Cases N=80 n (%)	Arm of Study: Controls N=80 n (%)	Total N=160n (%)	Chi Square Test	p-value
Gender	Male	59(73.8)	59(73.8)	118(73.8)	3.47	0.49
	Female	21(26.2)	21(26.2)	42(26.2)		
Age group/years	18-25	7(8.8)	5(6.3)	12(7.5)	7.430	0.115
	26-34	19(23.8)	19(23.8)	38(23.8)		
	35-44	20(25.0)	22(27.5)	42(26.3)		
	45-54	16(20.0)	19(23.8)	35(21.9)		
	≥55	18(22.5)	15(18.7)	33(20.6)		
Marital status	Single	32(40.0)	27(33.8)	59(36.9)	2.34	0.488
	Married	41(51.3)	49(61.3)	90(56.3)		
	Divorced	1(1.3)	1(1.3)	2(1.3)		
	Widowed	6(7.5)	3(3.7)	9(5.6)		
Education	None	4(5.0)	1(1.3)	5(3.1)	FET,7.435	0.125
	Primary	9(11.3)	3(3.7)	12(7.5)		
	Secondary	29(36.3)	25(31.3)	54(33.8)		
	Post-secondary	34(42.5)	48(60.0)	82(51.3)		
	Post graduate	4(5.0)	3(3.7)	7(4.4)		
Occupation	Unemployed	4(5.0)	5(6.3)	9(5.6)	FET,14.931	0.013*
	Trading	25(31.3)	12(15.0)	37(23.1)		
	Unskilled labour	14(17.5)	9(11.3)	23(14.4)		
	Professional	5(6.3)	14(17.5)	19(11.9)		
	Office worker	21(26.3)	28(35.0)	49(30.6)		
	House wife	0(0.0)	1(1.3)	1(0.6)		
	Student	9(11.3)	5(6.3)	14(8.8)		
	Farmer	2(2.5)	6(7.5)	8(5.0)		
Residence	Urban	51(63.7)	64(80.0)	115(71.9)	5.225	0.022*
	Rural	29(36.3	16(20.0)	45(28.1)		

*SD=Standard Deviation; *=statistically significant FET= Fischer Exact Test*

b) Comparison of RV structure and function amongst CLD patients and Controls

The RV basal dimension was the same in both arms (p = 1.000). The systolic function of the RV was not significantly different in the two arms (p = 0.283). The prevalence of right ventricular systolic dysfunction was 5% among the CLD patients and 1.2% among the

control subjects and showed no statistically significant difference between the two groups (p=0.124).

Mean PAP was significantly higher among those with CLD compared with the controls (21.3±10.1mmHg versus 14.1±7.6mmHg; p < 0.001). Four (5%) patients among the CLD group had elevated mPAP> 25mmHg with a mean of 26.5 ±3.1mmHg while there was none among the controls. The estimated pulmonary vascular resistance (PVR) was not significantly different between the cases and the controls (p > 0.05). PVR was found to be elevated(285dyne/sec/cm^{-5}) in only one person in the CLD group and none among the controls (Table 2).

Table 2: Relationship between Pulmonary Hypertension and Gender, Age and Aetiology of CLD

Variable	Pulmonary arterial Hypertension			Fisher's exact test	P=value
	Present (4)	Absent (76)	Total (80)		
Gender					
Male	1 (25)	58 (76.3)	59 (73.8)	5.169	0.053
Female	3 (75)	18 (23.7)	21 (26.3)		
Age					
≤ 25	0 (0)	7 (9.2)	7 (8.8)		
26-34	0 (0)	19 (25)	19 (23.8)	4.582	0.188
35-44	0 (0)	20 (26.3)	20 (25)		
45-54	2 (50)	14 (18.4)	16 (20)		
≥ 55	2 (50)	16 (21.1)	18 (22.5)		
Aetiology of CLD					
HBV	3 (75)	56 (73.7)	59 (73.8)		
HCV	1 (25)	12 (15.8)	13 (16.3)	2.061	0.825
Alcohol	0 (0)	7 (9.2)	7 (8.8)		
HBV/HCV	0 (0)	1 (1.3)	1 (1.3)		

c) *Aetiology of CLD in Patients with Elevated mPAP*

Of the 4 patients with mPAP> 25mmHg, the M: F ratio was 1: 3, 75% were HBV positive and 25% were HCV positive. None had significant alcohol use. Three were in MELD class 2 and one in MELD class 1. None was in MELD class 3 (p > 0.05)(Table 3).

Table 3: Comparison of Right Ventricular Structure and Function among Patients with CLD and their Healthy Controls (N=160)

Variable	Cases N=80 (%)	Controls N=80 (%)	Total N=160 (%)	Statistical Test	P-value
RV TAPSE Mean TAPSE±SD (cm)	2.16±0.4	2.2±0.3		T-test,1.663	0.283
RV Systolic function					
Normal	76(95.0)	79(98.8)	155(96.8)	FET	0.124
Abnormal	4(5.0)	1(1.2)	5(3.2)		
mPAP category					
Normal	76(95.0)	80(100.0)	158(97.5)	FET	0.120
Abnormal	4(5.0)	0(0.0)	4(2.5)		
Mean of mPAP±SD (mmHg)	21.3±10.1	14.1±7.6	17.0±12.4	T-test, 3.832	<0.001*
RV basal dimension					
Normal	77(96.3)	76(95.0)	153(95.6)	FET,	1.000
Increased	3(3.6)	4(5.0)	7(4.4)		
Pulmonary vascular resistance					
Normal	79(98.8)	80(100.0)	159(99.4)	FET,1.393	1.000
Elevated	1(1.2)	0(0.0)	1(0.6)		

*SD=Standard Deviation; *=statistically significant; FET= Fischer Exact Test; TAPSE= Tricuspid Annular Plane Systolic Excursion; mPAP= mean Pulmonary Artery Pressure*

V. Discussion

PoPH is an uncommon component of PAH. In the USA and Europe, the prevalence of PAH ranges from 15-50 per million with PoPH accounting for 5-15% of all cases of PAH.[17] McDonnell et al[18] reported that patients with hepatic cirrhosis had a low prevalence of PAH (0.73%) which corroborates the 1.25% found in this study. However, the prevalence appears to increase with the severity of liver disease and reaches approximately 5% amongst patients on a liver transplantation waiting list.[19]

Although mPAP was significantly higher in patients with CLD compared to those without CLD, the mean PVR showed no significant difference between the two arms of the study. This implies that hyper-dynamic circulation rather than a primary disorder of the pulmonary vessels was the underlying mechanism for the pulmonary hypertension in CLD patients.[7]The most common documented hemodynamic pattern in CLD patients with clinically significant PoH is peripheral vasodilatation and high cardiac output characterized by majorly, an increase in mPAP[8]

HBV is the most common cause of CLD in Nigeria and has been documented in other studies.[20,21] This study showed that more patients with HBV infection compared to HCV infection had PoPH but the difference was not statistically significant. HCV infection has been shown to be associated with decreased risk of PoPH[22] Female gender is associated with increased risk of PoP Hand is similar to findings in this study which documented PAH in more females than males although the difference was not statistically significant. Endogenous sex hormones particularly 17β oestradiol and its metabolites, have been implicated in the development of PAH.[23]

Evaluation of RV systolic function has become increasingly important in CLD patients as detection of subclinical RV dysfunction correlates positively with adverse clinical outcomes.[24]

RV systolic function assessment using TAPSE did not show any significant difference between the study and control groups and is similar to what was previously reported.[25] However, application of a new echo cardiographic modality known as speckle tracking in assessment of RV dysfunction showed significantly reduced RV total longitudinal strain was related to the severity of liver disease.[26]This highlights the usefulness of newer echo cardiographic modalities in evaluation of RV dysfunction in CLD.

Although right atrial catheterization remains gold standard for the diagnosis of PoPH, it is invasive and not readily available in our practice. TTE is a non-invasive, readily available modality for screening PoPH. A Cochrane systematic review and meta-analysis to evaluate the diagnostic accuracy of TTE in patients with PAH reported a sensitivity and specificity of 88% and 90% respectively in those without definitive lung disease.[27]

VI. Conclusion

The prevalence of PoPH was low in our CLD cohort and most of these patients had HBV-related CLD. TTE is a reliable method of screening forPoPHin CLD patients. Further studies are needed to identify symptoms, associations and prognosis of PoPH in our environment where liver transplantation is not readily available

VII. Limitation

Patients without clinically significant portal hypertension were not excluded from the study because of financial constraints in conducting additional investigations necessary to make that diagnosis. Secondly, Right atrial catheterization was not done because of its unavailability.

Declarations

Ethical Approval

Ethical approval was obtained from the Health Research Ethics Committee (HREC) of the University of Calabar Teaching Hospital, Calabar with protocol number UCTH/HREC/33/596

Consent for publication- Not applicable

Data Availability

The data supporting our findings are available from the corresponding author on reasonable request.

Competing interest: The authors declare no competing interests

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Clinical Trial Number – Not Applicable.

Authors' Contributions

UN contributed to the design of the study, data collection and analysis and wrote the original manuscript. UO contributed to literature review, discussion and wrote the final draft of the manuscript. VA contributed to concept, study design and supervision of the study. CO contributed to concept and study supervision. All authors read and approved the final manuscript and gave their consent for publication.

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