Research Article

Portopulmonary hypertension in a sample of Iraqi patients with chronic liver disease and portal hypertension

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ABSTRACT

INTRODUCTION: Portopulmonary hypertension is one of the most important complications in patients with chronic liver disease causing increased morbidity, mortality and sometimes a contraindication to liver transplantation, which is defined as an elevated pulmonary artery pressure due to increased resistance to blood flow in the setting of portal hypertension.

OBJECTIVE: This study aims at assessing the prevalence of pulmonary hypertension in a selected sample of chronic liver disease patients with portal hypertension and to search for an association between its development and some demographic and clinical features.

METHODS: An analytic-cross sectional study was conducted at Al-Imamain Al-Kadhmain Teaching Hospital in Baghdad from March 2019 to March 2020. Patients with portal hypertension (34) were enrolled and screened for pulmonary hypertension by transthoracic echocardiography for estimating the mean pulmonary artery pressure. The Child-Pugh score was used to assess the severity of the liver disease.

RESULTS: Out of thirty-four patients, 9 were females and 25 males with portal hypertension included in this study, pulmonary hypertension which is assessed by echocardiography has been detected in sixteen (16) patients (47.05%), (75%) of patients in class A of Child-Pugh score had pulmonary hypertension, (45%) of class B had pulmonary hypertension, while class C had 42%.

CONCLUSION: Pulmonary hypertension is reported in patients with CLD and portal hypertension. Age has a statistically significant association with development of pulmonary hypertension; however, the severity of CLD calculated by Child-Pugh score has shown no statistical association.

Key words: Portopulmonary hypertension, chronic liver disease, Child-Pugh score, portal hypertension .

INTRODUCTION

Portal hypertension is one of many complications that may develop in patients with chronic liver disease (CLD) leading to significant morbidity and mortality. Portopulmonary hypertension (PoPH) and hepatopulmonary syndrome (HPS) are two pulmonary vascular complications associated with CLD resulting in significant morbidity and mortality, particularly, in the setting of end-stage liver disease requiring liver transplantation (LT).[1]

Hepatopulmonary syndrome is characterized by intrapulmonary vascular dilatation and hypoxaemia, while portopulmonary hypertension (PoPH) is characterized by vasoconstriction, increased pulmonary vascular resistance (PVR) and increased mean pulmonary arterial pressures (mPAP), resulting in pulmonary arterial hypertension (PAH) in association with portal hypertension, with or without advanced chronic liver disease.[2]

Portopulmonary hypertension was initially described in 1951 by Mantz and Craige. The original description was mainly of academic interest because management options for end-stage liver disease (ESLD) were limited. However, the advent of liver transplantation (LT) significantly increases the recognition of portopulmonary hypertension as a complication of end-stage liver disease (ESLD) as well as the

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Table 1 | Child-Pugh score of severity of chronic liver disease

Clinical and lab criteria	Points		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretics responsive)	Severe (diuretic refractory)
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3.5	3.5-2.8	<2.8
Prothrombin time	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

Class A = 5-6 points, least severe liver disease; Class B = 7-9 points, moderately severe liver disease; Class C = 10-15 points, most severe liver disease

use of therapies to optimize its management to potentially allow for a liver transplant.[3]

Portal hypertension is usually confirmed by finding a sustained elevation of the mean pulmonary artery pressure more than 25 mmHg at rest, pulmonary vascular resistance more than > 240 dynes/s/cm^{-5} or 3 woods unit with a pulmonary capillary wedge pressure of < 15 mmHg and/or trans-pulmonary gradient > 12 mmHg.[4] While, portal hypertension is defined invasively as a hepatic venous pressure gradient (HVPG) of > 5 mmHg. Clinically, portal hypertension can be diagnosed by the presence of its complications like ascites, splenomegaly, oesophageal varices, and encephalopathy.[5]

Dyspnea on exertion is the most common initial presenting symptoms. Other symptoms include fatigue, generalized weakness, light-headedness, and orthopnea. Physical examination may show signs suggestive of pulmonary hypertension like elevated jugular venous pressure (JVP), loud P2, a murmur of tricuspid regurgitation and pulsatile liver, in addition to signs of the underlying chronic liver disease.[6]

It is thought that the candidate in the pathogenesis and pathophysiology of portopulmonary Hypertension is the abnormal regulation of serotonin and endothilin-1 (ET-1) in cases of portal hypertension; both are potent pulmonary vasoconstrictive neurohormones that may cause significant vascular remodelling changes and mitogenesis in the pulmonary arteries. At the same time, the production of vasodilator mediators such as nitric oxide and prostacyclin may be decreased in PoPH, facilitating the vascular remodelling and the proliferative vascular response.[7]

Classification of pulmonary hypertension: The 2003 World Health Organization (WHO) classification has been expanded to five groups, to emphasize the importance of the underlying cause of the disease:[4]

Group 1: Idiopathic pulmonary hypertension.

Group 2: Pulmonary hypertension due to left sided-heart disease.

Group 3: Pulmonary hypertension due to lung disease and/or chronic hypoxia.

Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH).

Group 5: Pulmonary hypertension due to blood and other disorders which include portal hypertension due to chronic liver disease.

Child-Pugh score[2] is a system for assessing the severity of chronic liver disease and prognosis, including the required treatment and necessity of liver transplant of chronic liver disease, primarily cirrhosis, as shown in table 1.

In Iraq, LT is not done locally with a project to start this therapy shortly. And as PoPH carries significant morbidity and mortality in patients scheduled for LT and because of rare reports talking about the prevalence of PoPH especially in our centre, we designed this study to detect the prevalence of PoPH in a group of patients with portal hypertension and chronic liver disease who are visiting the Gastroenterology Department at Al-Imamain Al-Kadhmain

Teaching Hospital in Baghdad. In addition to search for an association between its development and some demographic and clinical features.

METHODS

Study Design and Setting: This is an analytic cross-sectional study carried out at the Department of Gastroenterology, Al-Imamain Al-Kadhmain Teaching Hospital at Al-Kadhmia City, Al-Karkh district of Baghdad from March 2019 to March 2020.

Ethical considerations: The study was approved by the research committee of the Al-Karkh Health Directorate and agreed upon by the hospital administration. We explained the aims of the study to all participants before taking their consents. During all stages of the study data were kept confidential and were not used but for this study and in accordance with the code of ethics in research approved by the Ministry of Health in Iraq.

Case definition inclusion and exclusion criteria: We included patients diagnosed with chronic liver disease with portal hypertension in this study. ***Chronic liver disease*** was diagnosed by a consultant gastroenterologist based on clinical, laboratory and imaging examination. For sake of this study, ***portal hypertension*** was diagnosed either by the presence of its complications like ascites and splenomegaly proved by abdominal ultrasound examination and/or oesophageal varices proved by esophagogastroscopy if clinical features were suggestive, or by doppler study for intra and extrahepatic vessels; the increase diameter of portal vessels above 15 mmHg in addition to portal venous pressure above 14 cm H2O and acceleration waveform peaks were considered diagnostic for portal hypertension.[5]

Patients with a history of heart failure, chronic lung disease or connective tissue diseases that are known to be associated with pulmonary hypertension such as systemic sclerosis (SSc), mixed connective tissue disease and systemic lupus erythematosus were excluded from this study. Whenever indicated abdominal ultrasound and doppler examination was done by an experienced ultra-sonographer who used Philips HD 11 ultrasonographic machine.

Clinical examination and data collection: Data were collected from all patients by comprehensive history taking and thorough physical examination, in addition to virology screen, liver function tests and enzymes, abdominal ultrasound Doppler study, Oesophagogastroduodenoscopy (OGD), spirometry, electrocardiography and echocardiography. The aim was to prove the inclusion and exclusion criteria, identify the demographic features, assess the cause and severity of the liver disease. Then patients were grouped into two; those with pulmonary hypertension and those without. For each group age, gender, marital status, co-morbid illness and cause of liver disease were reported. Then association between these features and the development of pulmonary hypertension was searched for.

Outcomes: all enrolled patients have undergone an echocardiographic examination by a consultant cardiologist using E9 series of Vivid version GE machine to exclude left ventricular systolic dysfunction and to diagnosed pulmonary hypertension that was considered present when the mean pulmonary artery pressure (mPAP) is > 25 mmHg during rest or > 30 mmHg on exertion.[8] mPAP was measured by the simplified Bernoulli equation using a continuous wave Doppler measuring the peak TR velocity as the mean PAP = {4 x (maxTR vel)^2}.[8] Assessment of severity of liver disease for all participants was done using the Child-Pugh score.[2]

Statistical analysis: The collected data were organized, tabulated and statistically analysed using the Statistical Package for Social Science (SPSS) version 23. For numerical data, mean ±SD was measured while percentages were used for categorical variables. For the parametric variable, Pearson correlation coefficient was used, while for the non-parametric variables, Spearman correlation coefficient was used. P-values < 0.05 were considered statistically significant.

Table 2 | Demographic distribution of patients with chronic liver disease and portal hypertension

Patients with chronic liver disease and portal hypertension		With pulmonary hypertension		Without Pulmonary Hypertension		Total
		Number	%	Number	%	
Age mean in years		60 ± 15 years		36 ± 14		
Gender	Male	13	38.2	12	35.3	34
	Female	3	8.8	6	17.6	
Smoking	Yes	4	11.7	6	17.6	34
	No	12	35.3	6	17.6	
Marital status	Married	15	44.1	14	41.1	34
	Unmarried	1	2.9	4	11.7	
Diabetes mellitus	Yes	8	23.5	3	8.8	34
	No	8	23.5	15	44.1	
Hypertension	Yes	1	2.9	4	11.7	34
	No	15	44.1	14	41.1	
Causes of chronic liver disease	Alcohol	3	8.8	6	17.6	
	NASH	5	14.7	4	11.7	
	Viral	2	5.8	7	20.5	
	Auto-immune	0	0	2	5.8	
	Unknown	3	8.8	2	5.8	

RESULTS

Out of 34 patients with CLD and portal hypertension, 16 have pulmonary hypertension (47 %) as diagnosed by echocardiography. Nine patients (26.5%) were females and twenty-five were males (73.5%), 16 of male patients have pulmonary hypertension while only 3 of females having it. The age range in female was 43-70 years, the mean is 55.66 ± 8.54 years, while the age range in male was 22-75 years with a mean of 50.28 ± 14.50 years. The age of patients with pulmonary hypertension ranges from 55-75 years, mean of 60 ± 15 years. While for those without pulmonary hypertension it ranges from 22-50 years with a mean of 36 ± 14years.

The majority of patients participating in this study are married and they constituted 79.4% (being 64.7% with pulmonary hypertension and 14.7% without). All of the females are non-smokers, nine of males (36% of them) are smokers, 3 (8.8%) of them being with pulmonary Hypertension. Alcohol consumption is reported in 9 males (30%), and none in female patients drink alcohol, 3 (11.7%) of them have pulmonary hypertension. Diabetes mellitus has been shown by 11 (32.35%) of the study participants, 8 (23.5%) of them having pulmonary Hypertension. See Table 2

Table 3 shows the association between hav-

Table 3 | Shows the association between demographic parameters and pulmonary hypertension in patients with chronic liver disease and portal hypertension

Parameters		With PHT*	Without PHT*	P value
Age	Mean of age	60 ± 15	36 ± 14	0.0001
Gender				0.3360
	Male	13	12	
	Female	3	6	
Smoking				0.1718
	Yes	4	6	
	No	12	6	
Diabetes Mellitus				0.2340
	Yes	8	3	
	No	8	15	
Hypertension				0.1893
	Yes	1	4	
	No	15	14	
Causes				
	Alcohol	3	6	0.724
	NASH	5	4	0.212
	VIRAL	2	7	0.248
	Auto-immune	0	2	0.898
	Unknown	3	2	0.714

*PHT: Pulmonary hypertension

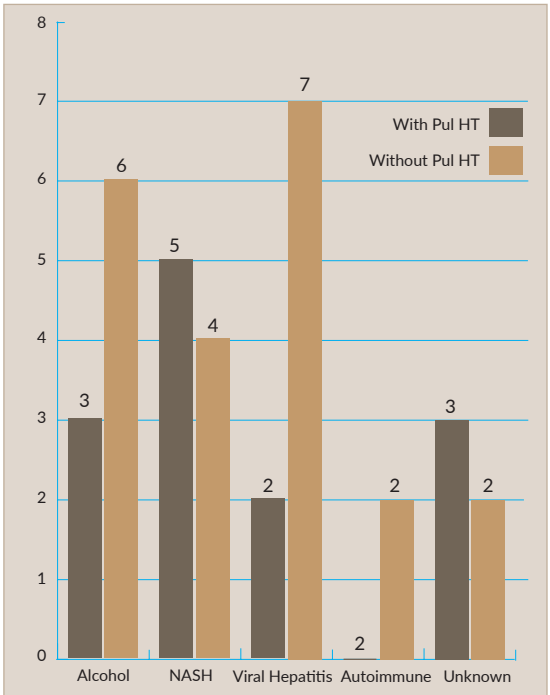

Figure 1 | Pulmonary hypertension in relation to the cause of chronic liver disease.

ing pulmonary hypertension and some demo-clinical features. Only age were shown to have a statistically significant association for the development of pulmonary hypertension.

Figure 1 shows the number of cases with pulmonary hypertension according to causes of chronic liver disease. The majority of patients with chronic liver disease are alcoholic in 9 patients, viral in 8 patients, then non-alcoholic steatohepatitis (NASH) in 8 patients.

Child –Pugh Score for patients with or without pulmonary hypertension is shown in table 4. The severity of chronic liver disease has no statistical significance on the development of pulmonary hypertension.

DISCUSSION

Portopulmonary hypertension is now considered an uncommon complication of portal hypertension with or without chronic liver disease and it is a contraindication to liver transplantation and transjugular intrahepatic portosystemic shunt when severe.[9]

Table 3 | Child-Pugh Score according to class and pulmonary hypertension

Child-Pugh Score	With PHT	Without PHT	Total	P value
Total class A	3 (75%)	1 (25%)	4	
Total class B	5 (45%)	6 (55%)	11	
Total class C	8 (42%)	11 (58%)	19	
Grand Total	16 (47%)	18 (53%)	34	0.4838

*PHT: Pulmonary hypertension

Echocardiography is a highly sensitive tool for the detection of pulmonary hypertension and assessing severity, but it has to be confirmed by right heart catheterization.[8]

A study in Toronto General Hospital showed that the prevalence of portopulmonary hypertension is 16.1% among a sample of 62 patients with decompensated cirrhosis and refractory ascites.[7] Another study in France showed that 17 out of 165 (10.3%) among patients with end-stage liver disease who evaluated for liver transplantation has portopulmonary hypertension assessed by Doppler echocardiography. Portopulmonary hypertension was confirmed by catheterization in 10 patients and ruled out in 7. There were no false negatives of echocardiography and concluded that Doppler echocardiography is a highly sensitive tool but less specific for detecting portopulmonary hypertension.[9]

The prevalence of portopulmonary hypertension depends on the patient population studies and severity of the liver disease, 0.7–2% and 3.5–16.1% in cirrhotics and patients undergoing liver transplantation, respectively.[10]

In this study, out of 34 participants with chronic liver disease and portal hypertension, pulmonary hypertension was detected in 16 participants (47%). This percentage is higher than expected and this can be attributed to the small sample size and more severity of patients as most of our participants were hospitalized due to liver decompensation and complications. Lack of confirmatory right heart catheterization in our series may overestimate pulmonary hypertension by including patients with other causes of pulmonary hypertension. Although we have excluded patients with concomitant heart or lung disease, still when we

look at the definition of portopulmonary hypertension, besides the estimated mean pulmonary arterial pressure (>25mmHg) we must also have pulmonary vascular resistance of more than 3 wood units and pulmonary capillary wedge pressure (PCWP) of less than 15 mmHg to exclude volume overload and high cardiac output; the accurate measurements of these parameters requires invasive procedures. So this percentage reflects different causes of pulmonary hypertension as well as portopulmoanry hypertension, which may indicate that these patients are undertreated for volume overload and possibly due to noncompliance with medical therapy.

There was no correlation noted between the severity of liver disease according to Child-Pugh score and the development or severity of pulmonary hypertension. Which is consistent with the result of another similar study.[10]

We found a correlation between age and development of pulmonary hypertension in patients with chronic liver disease, incidence of pulmonary hypertension is more with increasing age. This finding is consistent with a study done by Al-Busafi and published in the International Journal of Hepatology 2012 that showed a significant correlation between the age and the development of pulmonary hypertension in a patient with chronic liver disease.[11]

Portopulmonary hypertension in our study was observed more in males than females, 47% and 8.8%, respectively. This can be explained by the fact that number of males in our sample out-weighted that of women (25 versus 9), also males drink alcohol much more common than females in oriental countries like Iraq. On the contrary, a multicenter case-control study conducted by Kawut on 34 cases with advanced liver disease and 141 controls with normal echocardiography has found that the female gender was associated with a higher risk of PoPH than the male sex (p = 0.018). He concluded that hormonal and immunologic factors may be integral factors for the development of PoPH.[7]

We found that non-alcoholic steatohepatitis is the cause of CLD with portopulmonary hypertension in 5 patients (3 males and 2 females, alcoholic liver cirrhosis in 3 males, viral hepatitis in 2, and the cause was unknown in 3 patients. Non of them were having autoimmune liver cirrhosis. Krowka has shown similarly that non-alcoholic steatohepatitis is more common in patients with portopulmonary hypertension and chronic liver disease.[9]

This study has many limitations; the sample size was small due to limited time and resources. In addition, invasive procedure like angiography to diagnose accurately pulmonary hypertension and its cause was not routinely performed in our department as liver transplantation is not used in the treatment of patients with end stage liver disease.

CONCLUSION

Pulmonary hypertension is more prevalent among patients with CLD disease than we expected. Age of the patient has shown a statistically significant association with the development of pulmonary hypertension in patients with CLD and portal hypertension; however, the severity of CLD calculated by Child-Pugh score has shown no statistical association.

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Abbreviations list: Centimetre water (**cm H2O**), Chronic liver disease (**CLD**), Chronic thromboembolic pulmonary hypertension (**CTEPH**), Endothilin-1 (**ET-1**), End-stage liver disease (**ESLD**), Hepatic venous pressure gradient (**HVPG**), Hepatopulmonary syndrome (**HPS**), Jugular venous pressure (**JVP**), Liver transplantation (**LT**), Mean pulmonary arterial pressures (**mPAP**), Millimetre Mercury (**mmHg**), Non-alcoholic steatohepatitis (**NASH**), Oesophagogastroduodenoscopy (**OGD**), Portopulmonary hypertension (**PoPH**), Pulmonary arterial hypertension (**PAH**), Pulmonary capillary wedge pressure (**PCWP**), Pulmonary vascular resistance (**PVR**), Standard deviation (**SD**), Statistical Package for Social Science (**SPSS**), Systemic sclerosis (**SSc**), World Health Organization (**WHO**).

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